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(71) Applicant *(for all designated States except US)*: **GENOMATICA, INC.** [US/US]; 5405 Morehouse Drive, Suite 210, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PALSSON, Bernhard, O.** [US/US]; 730 Fern Glen, La Jolla, CA 92037 (US). **FAMILI, Imandokht** [US/US]; 10185 Camino Ruiz #132, San Diego, CA 92126 (US). **COVERT, Markus, W.** [US/US]; 3353 Lebon Drive, #302, San Diego, CA 92122 (US). **SCHILLING, Christophe, H.** [US/US]; 12541-G El Camino Real, San Diego, CA 92130 (US).

(74) Agents: **GAY, David, A.** et al.; McDermott, Will & Emery, 4370 La Jolla Village Drive, 7th Floor, San Diego, CA 92122 (US).

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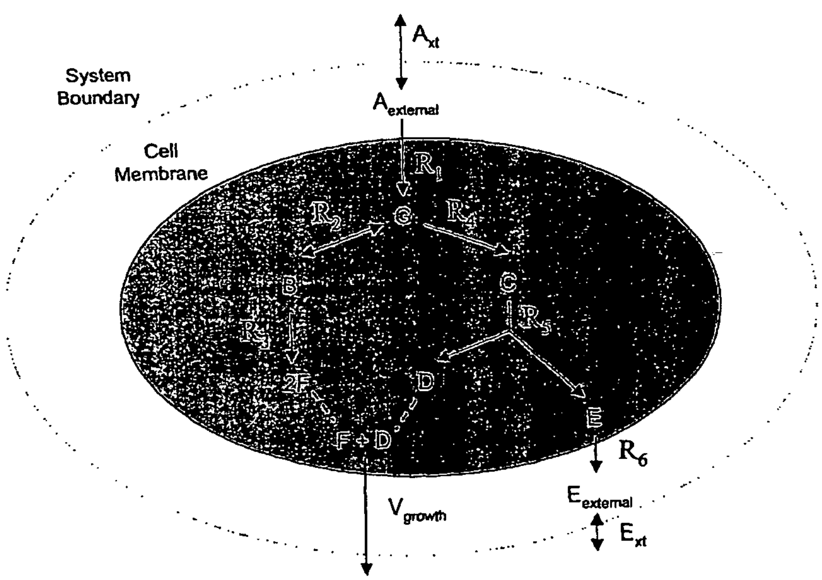
(54) Title: HUMAN METABOLIC MODELS AND METHODS



(57) Abstract: The invention provides in silico models for determining the physiological function of human cells, including human skeletal muscle cells. The models include a data structure relating a plurality of *Homo sapiens* reactions, a constraint set for the plurality of *Homo sapiens* reactions, and commands for determining a distribution of flux through the reactions that is predictive of a *Homo sapiens* physiological function. A model of the invention can further include a gene database containing information characterizing the associated gene or genes. A regulated *Homo sapiens* reaction can be represented in a model of the invention by including a variable constraint for the regulated reaction. The invention further provides methods for making an *in silico Homo sapiens* physiological function using a model of the invention.

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HUMAN METABOLIC MODELS AND METHODS

BACKGROUND OF THE INVENTION

This invention relates generally to analysis of the activity of chemical reaction networks and, more specifically, to computational methods for simulating and predicting the activity of *Homo sapiens* reaction networks.

Therapeutic agents, including drugs and gene-based agents, are being rapidly developed by the pharmaceutical industry with the goal of preventing or treating human disease. Dietary supplements, including herbal products, vitamins and amino acids, are also being developed and marketed by the nutraceutical industry. Because of the complexity of the biochemical reaction networks in and between human cells, even relatively minor perturbations caused by a therapeutic agent or a dietary component in the abundance or activity of a particular target, such as a metabolite, gene or protein, can affect hundreds of biochemical reactions. These perturbations can lead to desirable therapeutic effects, such as cell stasis or cell death in the case of cancer cells or other pathologically hyperproliferative cells. However, these perturbations can also lead to undesirable side effects, such as production of toxic byproducts, if the systemic effects of the perturbations are not taken into account.

Current approaches to drug and nutraceutical development do not take into account the effect of a perturbation in a molecular target on systemic cellular behavior. In order to design effective methods of

repairing, engineering or disabling cellular activities, it is essential to understand human cellular behavior from an integrated perspective.

Cellular metabolism, which is an example of a process involving a highly integrated network of biochemical reactions, is fundamental to all normal cellular or physiological processes, including homeostatis, proliferation, differentiation, programmed cell death (apoptosis) and motility. Alterations in cellular metabolism characterize a vast number of human diseases. For example, tissue injury is often characterized by increased catabolism of glucose, fatty acids and amino acids, which, if persistent, can lead to organ dysfunction. Conditions of low oxygen supply (hypoxia) and nutrient supply, such as occur in solid tumors, result in a myriad of adaptive metabolic changes including activation of glycolysis and neovascularization. Metabolic dysfunctions also contribute to neurodegenerative diseases, cardiovascular disease, neuromuscular diseases, obesity and diabetes. Currently, despite the importance of cellular metabolism to normal and pathological processes, a detailed systemic understanding of cellular metabolism in human cells is currently lacking.

Thus, there exists a need for models that describe *Homo sapiens* reaction networks, including core metabolic reaction networks and metabolic reaction networks in specialized cell types, which can be used to simulate different aspects of human cellular behavior under physiological, pathological and therapeutic conditions. The present invention satisfies this need, and provides related advantages as well.

SUMMARY OF THE INVENTION

The invention provides a computer readable medium or media, including: (a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, (b) a constraint set for the plurality of *Homo sapiens* reactions, and (c) commands for determining at least one flux distribution that minimizes or maximizes an objective function when the constraint set is applied to the data representation, wherein the at least one flux distribution is predictive of a *Homo sapiens* physiological function. In one embodiment, at least one of the *Homo sapiens* reactions in the data structure is annotated to indicate an associated gene and the computer readable medium or media further includes a gene database including information characterizing the associated gene. In another embodiment, at least one of the *Homo sapiens* reactions is a regulated reaction and the computer readable medium or media further includes a constraint set for the plurality of *Homo sapiens* reactions, wherein the constraint set includes a variable constraint for the regulated reaction.

The invention provides a method for predicting a *Homo sapiens* physiological function, including: (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo*

sapiens reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product; (b) providing a constraint set for the plurality of *Homo sapiens* reactions; (c) providing an objective function, and (d) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function. In one embodiment, at least one of the *Homo sapiens* reactions in the data structure is annotated to indicate an associated gene and the method predicts a *Homo sapiens* physiological function related to the gene.

The invention provides a method for predicting a *Homo sapiens* physiological function, including: (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, wherein at least one of the *Homo sapiens* reactions is a regulated reaction; (b) providing a constraint set for the plurality of *Homo sapiens* reactions, wherein the constraint set includes a variable constraint for the regulated reaction; (c) providing a condition-dependent value to the variable constraint; (d) providing an objective function, and (e) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied

to the data structure, thereby predicting a *Homo sapiens* physiological function.

Also provided by the invention is a method for making a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions in a computer readable medium or media, including: (a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of the *Homo sapiens* reactions; (b) relating the plurality of *Homo sapiens* reactants to the plurality of *Homo sapiens* reactions in a data structure, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product; (c) determining a constraint set for the plurality of *Homo sapiens* reactions; (d) providing an objective function; (e) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, and (f) if the at least one flux distribution is not predictive of a *Homo sapiens* physiological function, then adding a reaction to or deleting a reaction from the data structure and repeating step (e), if the at least one flux distribution is predictive of a *Homo sapiens* physiological function, then storing the data structure in a computer readable medium or media. The invention further provides a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein the data structure is produced by the method.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic representation of a hypothetical metabolic network.

Figure 2 shows mass balance constraints and flux constraints (reversibility constraints) that can be placed on the hypothetical metabolic network shown in Figure 1.

Figure 3 shows the stoichiometric matrix (S) for the hypothetical metabolic network shown in Figure 1.

Figure 4 shows, in Panel A, an exemplary biochemical reaction network and in Panel B, an exemplary regulatory control structure for the reaction network in panel A.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides *in silico* models that describe the interconnections between genes in the *Homo sapiens* genome and their associated reactions and reactants. The models can be used to simulate different aspects of the cellular behavior of human cells under different normal, pathological and therapeutic conditions, thereby providing valuable information for therapeutic, diagnostic and research applications. An advantage of the models of the invention is that they provide a holistic approach to simulating and predicting the activity of *Homo sapiens* cells. The models and methods can also be extended to simulate the activity of multiple interacting cells,

including organs, physiological systems and whole body metabolism.

As an example, the *Homo sapiens* metabolic models of the invention can be used to determine the effects of changes from aerobic to anaerobic conditions, such as occurs in skeletal muscles during exercise or in tumors, or to determine the effect of various dietary changes. The *Homo sapiens* metabolic models can also be used to determine the consequences of genetic defects, such as deficiencies in metabolic enzymes such as phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase and adenosine deaminase.

The *Homo sapiens* metabolic models can also be used to choose appropriate targets for drug design. Such targets include genes, proteins or reactants, which when modulated positively or negatively in a simulation produce a desired therapeutic result. The models and methods of the invention can also be used to predict the effects of a therapeutic agent or dietary supplement on a cellular function of interest. Likewise, the models and methods can be used to predict both desirable and undesirable side effects of the therapeutic agent on an interrelated cellular function in the target cell, as well as the desirable and undesirable effects that may occur in other cell types. Thus, the models and methods of the invention can make the drug development process more rapid and cost effective than is currently possible.

The *Homo sapiens* metabolic models can also be used to predict or validate the assignment of particular biochemical reactions to the enzyme-encoding genes found in the genome, and to identify the presence

of reactions or pathways not indicated by current genomic data. Thus, the models can be used to guide the research and discovery process, potentially leading to the identification of new enzymes, medicines or metabolites of clinical importance.

The models of the invention are based on a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product. The reactions included in the data structure can be those that are common to all or most *Homo sapiens* cells, such as core metabolic reactions, or reactions specific for one or more given cell type.

As used herein, the term "*Homo sapiens* reaction" is intended to mean a conversion that consumes a substrate or forms a product that occurs in or by a *Homo sapiens* cell. The term can include a conversion that occurs due to the activity of one or more enzymes that are genetically encoded by a *Homo sapiens* genome. The term can also include a conversion that occurs spontaneously in a *Homo sapiens* cell. Conversions included in the term include, for example, changes in chemical composition such as those due to nucleophilic or electrophilic addition, nucleophilic or electrophilic substitution, elimination, isomerization, deamination, phosphorylation, methylation, reduction, oxidation or changes in location such as those that occur due to a transport reaction that moves a reactant from one cellular compartment to another. In the case of a transport reaction, the substrate and product of

the reaction can be chemically the same and the substrate and product can be differentiated according to location in a particular cellular compartment. Thus, a reaction that transports a chemically unchanged reactant from a first compartment to a second compartment has as its substrate the reactant in the first compartment and as its product the reactant in the second compartment. It will be understood that when used in reference to an *in silico* model or data structure, a reaction is intended to be a representation of a chemical conversion that consumes a substrate or produces a product.

As used herein, the term "*Homo sapiens* reactant" is intended to mean a chemical that is a substrate or a product of a reaction that occurs in or by a *Homo sapiens* cell. The term can include substrates or products of reactions performed by one or more enzymes encoded by a *Homo sapiens* genome, reactions occurring in *Homo sapiens* that are performed by one or more non-genetically encoded macromolecule, protein or enzyme, or reactions that occur spontaneously in a *Homo sapiens* cell. Metabolites are understood to be reactants within the meaning of the term. It will be understood that when used in reference to an *in silico* model or data structure, a reactant is intended to be a representation of a chemical that is a substrate or a product of a reaction that occurs in or by a *Homo sapiens* cell.

As used herein the term "substrate" is intended to mean a reactant that can be converted to one or more products by a reaction. The term can include, for example, a reactant that is to be chemically changed due to nucleophilic or electrophilic

addition, nucleophilic or electrophilic substitution, elimination, isomerization, deamination, phosphorylation, methylation, reduction, oxidation or that is to change location such as by being transported across a membrane or to a different compartment.

As used herein, the term "product" is intended to mean a reactant that results from a reaction with one or more substrates. The term can include, for example, a reactant that has been chemically changed due to nucleophilic or electrophilic addition, nucleophilic or electrophilic substitution, elimination, isomerization, deamination, phosphorylation, methylation, reduction or oxidation or that has changed location such as by being transported across a membrane or to a different compartment.

As used herein, the term "stoichiometric coefficient" is intended to mean a numerical constant correlating the number of one or more reactants and the number of one or more products in a chemical reaction. Typically, the numbers are integers as they denote the number of molecules of each reactant in an elementally balanced chemical equation that describes the corresponding conversion. However, in some cases the numbers can take on non-integer values, for example, when used in a lumped reaction or to reflect empirical data.

As used herein, the term "plurality," when used in reference to *Homo sapiens* reactions or reactants, is intended to mean at least 2 reactions or reactants. The term can include any number of *Homo sapiens* reactions or reactants in the range from 2 to the number of naturally occurring reactants or reactions for a particular of *Homo sapiens* cell. Thus,

the term can include, for example, at least 10, 20, 30, 50, 100, 150, 200, 300, 400, 500, 600 or more reactions or reactants. The number of reactions or reactants can be expressed as a portion of the total number of naturally occurring reactions for a particular *Homo sapiens* cell, such as at least 20%, 30%, 50%, 60%, 75%, 90%, 95% or 98% of the total number of naturally occurring reactions that occur in a particular *Homo sapiens* cell.

As used herein, the term "data structure" is intended to mean a physical or logical relationship among data elements, designed to support specific data manipulation functions. The term can include, for example, a list of data elements that can be added combined or otherwise manipulated such as a list of representations for reactions from which reactants can be related in a matrix or network. The term can also include a matrix that correlates data elements from two or more lists of information such as a matrix that correlates reactants to reactions. Information included in the term can represent, for example, a substrate or product of a chemical reaction, a chemical reaction relating one or more substrates to one or more products, a constraint placed on a reaction, or a stoichiometric coefficient.

As used herein, the term "constraint" is intended to mean an upper or lower boundary for a reaction. A boundary can specify a minimum or maximum flow of mass, electrons or energy through a reaction. A boundary can further specify directionality of a reaction. A boundary can be a constant value such as zero, infinity, or a numerical value such as an integer. Alternatively, a boundary can be a variable boundary value as set forth below.

As used herein, the term "variable," when used in reference to a constraint is intended to mean capable of assuming any of a set of values in response to being acted upon by a constraint function. The term "function," when used in the context of a constraint, is intended to be consistent with the meaning of the term as it is understood in the computer and mathematical arts. A function can be binary such that changes correspond to a reaction being off or on. Alternatively, continuous functions can be used such that changes in boundary values correspond to increases or decreases in activity. Such increases or decreases can also be binned or effectively digitized by a function capable of converting sets of values to discreet integer values. A function included in the term can correlate a boundary value with the presence, absence or amount of a biochemical reaction network participant such as a reactant, reaction, enzyme or gene. A function included in the term can correlate a boundary value with an outcome of at least one reaction in a reaction network that includes the reaction that is constrained by the boundary limit. A function included in the term can also correlate a boundary value with an environmental condition such as time, pH, temperature or redox potential.

As used herein, the term "activity," when used in reference to a reaction, is intended to mean the amount of product produced by the reaction, the amount of substrate consumed by the reaction or the rate at which a product is produced or a substrate is consumed. The amount of product produced by the reaction, the amount of substrate consumed by the reaction or the rate at which a product is produced or a substrate is consumed can also be referred to as the flux for the reaction.

As used herein, the term "activity," when used in reference to a *Homo sapiens* cell, is intended to mean the magnitude or rate of a change from an initial state to a final state. The term can include, for example, the amount of a chemical consumed or produced by a cell, the rate at which a chemical is consumed or produced by a cell, the amount or rate of growth of a cell or the amount of or rate at which energy, mass or electrons flow through a particular subset of reactions.

The invention provides a computer readable medium, having a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product.

Depending on the application, the plurality of *Homo sapiens* reactions can include reactions selected from core metabolic reactions or peripheral metabolic reactions. As used herein, the term "core," when used in reference to a metabolic pathway, is intended to mean a metabolic pathway selected from glycolysis/gluconeogenesis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, glycogen storage, electron transfer system (ETS), the malate/aspartate shuttle, the glycerol phosphate shuttle, and plasma and mitochondrial membrane transporters. As used herein, the term "peripheral," when used in reference to a metabolic pathway, is intended to mean a metabolic pathway that includes one or more reactions that are not a part of a core metabolic pathway.

A plurality of *Homo sapiens* reactants can be related to a plurality of *Homo sapiens* reactions in any data structure that represents, for each reactant, the reactions by which it is consumed or produced. Thus, the data structure, which is referred to herein as a "reaction network data structure," serves as a representation of a biological reaction network or system. An example of a reaction network that can be represented in a reaction network data structure of the invention is the collection of reactions that constitute the core metabolic reactions of *Homo sapiens*, or the metabolic reactions of a skeletal muscle cell, as shown in the Examples.

The choice of reactions to include in a particular reaction network data structure, from among all the possible reactions that can occur in human cells, depends on the cell type or types and the physiological, pathological or therapeutic condition being modeled, and can be determined experimentally or from the literature, as described further below.

The reactions to be included in a particular network data structure of *Homo sapiens* can be determined experimentally using, for example, gene or protein expression profiles, where the molecular characteristics of the cell can be correlated to the expression levels. The expression or lack of expression of genes or proteins in a cell type can be used in determining whether a reaction is included in the model by association to the expressed gene(s) and or protein(s). Thus, it is possible to use experimental technologies to determine which genes and/or proteins are expressed in a specific cell type, and to further use this information to determine which reactions are present in the cell type of interest. In

this way a subset of reactions from all of those reactions that can occur in human cells are selected to comprise the set of reactions that represent a specific cell type. cDNA expression profiles have been demonstrated to be useful, for example, for classification of breast cancer cells (Sorlie et al., Proc. Natl. Acad. Sci. U.S.A. 98(19):10869-10874 (2001)).

The methods and models of the invention can be applied to any *Homo sapiens* cell type at any stage of differentiation, including, for example, embryonic stem cells, hematopoietic stem cells, differentiated hematopoietic cells, skeletal muscle cells, cardiac muscle cells, smooth muscle cells, skin cells, nerve cells, kidney cells, pulmonary cells, liver cells, adipocytes and endocrine cells (e.g. beta islet cells of the pancreas, mammary gland cells, adrenal cells, and other specialized hormone secreting cells).

The methods and models of the invention can be applied to normal cells or pathological cells. Normal cells that exhibit a variety of physiological activities of interest, including homeostasis, proliferation, differentiation, apoptosis, contraction and motility, can be modeled. Pathological cells can also be modeled, including cells that reflect genetic or developmental abnormalities, nutritional deficiencies, environmental assaults, infection (such as by bacteria, viral, protozoan or fungal agents), neoplasia, aging, altered immune or endocrine function, tissue damage, or any combination of these factors. The pathological cells can be representative of any type of human pathology, including, for example, various metabolic disorders of carbohydrate, lipid or protein metabolism, obesity, diabetes, cardiovascular

disease, fibrosis, various cancers, kidney failure, immune pathologies, neurodegenerative diseases, and various monogenetic metabolic diseases described in the Online Mendelian Inheritance in Man database (Center for Medical Genetics, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD)).

The methods and models of the invention can also be applied to cells undergoing therapeutic perturbations, such as cells treated with drugs that target participants in a reaction network, cells treated with gene-based therapeutics that increase or decrease expression of an encoded protein, and cells treated with radiation. As used herein, the term "drug" refers to a compound of any molecular nature with a known or proposed therapeutic function, including, for example, small molecule compounds, peptides and other macromolecules, peptidomimetics and antibodies, any of which can optionally be tagged with cytostatic, targeting or detectable moieties. The term "gene-based therapeutic" refers to nucleic acid therapeutics, including, for example, expressible genes with normal or altered protein activity, antisense compounds, ribozymes, DNAzymes, RNA interference compounds (RNAi) and the like. The therapeutics can target any reaction network participant, in any cellular location, including participants in extracellular, cell surface, cytoplasmic, mitochondrial and nuclear locations. Experimental data that are gathered on the response of cells to therapeutic treatment, such as alterations in gene or protein expression profiles, can be used to tailor a network for a pathological state of a particular cell type.

The methods and models of the invention can be applied to *Homo sapiens* cells as they exist in any form, such as in primary cell isolates or in established cell lines, or in the whole body, in intact organs or in tissue explants. Accordingly, the methods and models can take into account intercellular communications and/or inter-organ communications, the effect of adhesion to a substrate or neighboring cells (such as a stem cell interacting with mesenchymal cells or a cancer cell interacting with its tissue microenvironment, or beta-islet cells without normal stroma), and other interactions relevant to multicellular systems.

The reactants to be used in a reaction network data structure of the invention can be obtained from or stored in a compound database. As used herein, the term "compound database" is intended to mean a computer readable medium or media containing a plurality of molecules that includes substrates and products of biological reactions. The plurality of molecules can include molecules found in multiple organisms, thereby constituting a universal compound database. Alternatively, the plurality of molecules can be limited to those that occur in a particular organism, thereby constituting an organism-specific compound database. Each reactant in a compound database can be identified according to the chemical species and the cellular compartment in which it is present. Thus, for example, a distinction can be made between glucose in the extracellular compartment versus glucose in the cytosol. Additionally each of the reactants can be specified as a metabolite of a primary or secondary metabolic pathway. Although identification of a reactant as a metabolite of a primary or secondary metabolic pathway does not

indicate any chemical distinction between the reactants in a reaction, such a designation can assist in visual representations of large networks of reactions.

As used herein, the term "compartment" is intended to mean a subdivided region containing at least one reactant, such that the reactant is separated from at least one other reactant in a second region. A subdivided region included in the term can be correlated with a subdivided region of a cell. Thus, a subdivided region included in the term can be, for example, the intracellular space of a cell; the extracellular space around a cell; the periplasmic space, the interior space of an organelle such as a mitochondrium, endoplasmic reticulum, Golgi apparatus, vacuole or nucleus; or any subcellular space that is separated from another by a membrane or other physical barrier. Subdivided regions can also be made in order to create virtual boundaries in a reaction network that are not correlated with physical barriers. Virtual boundaries can be made for the purpose of segmenting the reactions in a network into different compartments or substructures.

As used herein, the term "substructure" is intended to mean a portion of the information in a data structure that is separated from other information in the data structure such that the portion of information can be separately manipulated or analyzed. The term can include portions subdivided according to a biological function including, for example, information relevant to a particular metabolic pathway such as an internal flux pathway, exchange flux pathway, central metabolic pathway, peripheral metabolic pathway, or secondary metabolic pathway. The term can include portions subdivided according to computational or

mathematical principles that allow for a particular type of analysis or manipulation of the data structure.

The reactions included in a reaction network data structure can be obtained from a metabolic reaction database that includes the substrates, products, and stoichiometry of a plurality of metabolic reactions of *Homo sapiens*. The reactants in a reaction network data structure can be designated as either substrates or products of a particular reaction, each with a stoichiometric coefficient assigned to it to describe the chemical conversion taking place in the reaction. Each reaction is also described as occurring in either a reversible or irreversible direction. Reversible reactions can either be represented as one reaction that operates in both the forward and reverse direction or be decomposed into two irreversible reactions, one corresponding to the forward reaction and the other corresponding to the backward reaction.

Reactions included in a reaction network data structure can include intra-system or exchange reactions. Intra-system reactions are the chemically and electrically balanced interconversions of chemical species and transport processes, which serve to replenish or drain the relative amounts of certain metabolites. These intra-system reactions can be classified as either being transformations or translocations. A transformation is a reaction that contains distinct sets of compounds as substrates and products, while a translocation contains reactants located in different compartments. Thus a reaction that simply transports a metabolite from the extracellular environment to the cytosol, without changing its chemical composition is solely classified as a translocation, while a reaction that takes an

extracellular substrate and converts it into a cytosolic product is both a translocation and a transformation.

Exchange reactions are those which constitute sources and sinks, allowing the passage of metabolites into and out of a compartment or across a hypothetical system boundary. These reactions are included in a model for simulation purposes and represent the metabolic demands placed on *Homo sapiens*. While they may be chemically balanced in certain cases, they are typically not balanced and can often have only a single substrate or product. As a matter of convention the exchange reactions are further classified into demand exchange and input/output exchange reactions.

The metabolic demands placed on the *Homo sapiens* metabolic reaction network can be readily determined from the dry weight composition of the cell which is available in the published literature or which can be determined experimentally. The uptake rates and maintenance requirements for *Homo sapiens* cells can also be obtained from the published literature or determined experimentally.

Input/output exchange reactions are used to allow extracellular reactants to enter or exit the reaction network represented by a model of the invention. For each of the extracellular metabolites a corresponding input/output exchange reaction can be created. These reactions are always reversible with the metabolite indicated as a substrate with a stoichiometric coefficient of one and no products produced by the reaction. This particular convention is adopted to allow the reaction to take on a positive flux value (activity level) when the metabolite is

being produced or removed from the reaction network and a negative flux value when the metabolite is being consumed or introduced into the reaction network. These reactions will be further constrained during the course of a simulation to specify exactly which metabolites are available to the cell and which can be excreted by the cell.

A demand exchange reaction is always specified as an irreversible reaction containing at least one substrate. These reactions are typically formulated to represent the production of an intracellular metabolite by the metabolic network or the aggregate production of many reactants in balanced ratios such as in the representation of a reaction that leads to biomass formation, also referred to as growth.

A demand exchange reactions can be introduced for any metabolite in a model of the invention. Most commonly these reactions are introduced for metabolites that are required to be produced by the cell for the purposes of creating a new cell such as amino acids, nucleotides, phospholipids, and other biomass constituents, or metabolites that are to be produced for alternative purposes. Once these metabolites are identified, a demand exchange reaction that is irreversible and specifies the metabolite as a substrate with a stoichiometric coefficient of unity can be created. With these specifications, if the reaction is active it leads to the net production of the metabolite by the system meeting potential production demands. Examples of processes that can be represented as a demand exchange reaction in a reaction network data structure and analyzed by the methods of the invention include, for example, production or secretion of an individual protein; production or

secretion of an individual metabolite such as an amino acid, vitamin, nucleoside, antibiotic or surfactant; production of ATP for extraneous energy requiring processes such as locomotion; or formation of biomass constituents.

In addition to these demand exchange reactions that are placed on individual metabolites, demand exchange reactions that utilize multiple metabolites in defined stoichiometric ratios can be introduced. These reactions are referred to as aggregate demand exchange reactions. An example of an aggregate demand reaction is a reaction used to simulate the concurrent growth demands or production requirements associated with cell growth that are placed on a cell, for example, by simulating the formation of multiple biomass constituents simultaneously at a particular cellular growth rate.

A hypothetical reaction network is provided in Figure 1 to exemplify the above-described reactions and their interactions. The reactions can be represented in the exemplary data structure shown in Figure 3 as set forth below. The reaction network, shown in Figure 1, includes intrasystem reactions that occur entirely within the compartment indicated by the shaded oval such as reversible reaction R_2 which acts on reactants B and G and reaction R_3 which converts one equivalent of B to 2 equivalents of F. The reaction network shown in Figure 1 also contains exchange reactions such as input/output exchange reactions A_{xt} and E_{xt}, and the demand exchange reaction, V_{growth}, which represents growth in response to the one equivalent of D and one equivalent of F. Other intrasystem reactions include R_1 which is a translocation and transformation reaction that translocates reactant A into the

compartment and transforms it to reactant G and reaction R_6 which is a transport reaction that translocates reactant E out of the compartment.

A reaction network can be represented as a set of linear algebraic equations which can be presented as a stoichiometric matrix S, with S being an m x n matrix where m corresponds to the number of reactants or metabolites and n corresponds to the number of reactions taking place in the network. An example of a stoichiometric matrix representing the reaction network of Figure 1 is shown in Figure 3. As shown in Figure 3, each column in the matrix corresponds to a particular reaction n, each row corresponds to a particular reactant m, and each S_{mn} element corresponds to the stoichiometric coefficient of the reactant m in the reaction denoted n. The stoichiometric matrix includes intra-system reactions such as R_2 and R_3 which are related to reactants that participate in the respective reactions according to a stoichiometric coefficient having a sign indicative of whether the reactant is a substrate or product of the reaction and a value correlated with the number of equivalents of the reactant consumed or produced by the reaction. Exchange reactions such as $-E_{xt}$ and $-A_{xt}$ are similarly correlated with a stoichiometric coefficient. As exemplified by reactant E, the same compound can be treated separately as an internal reactant (E) and an external reactant ($E_{external}$) such that an exchange reaction (R_6) exporting the compound is correlated by stoichiometric coefficients of -1 and 1, respectively. However, because the compound is treated as a separate reactant by virtue of its compartmental location, a reaction, such as R_5, which produces the internal reactant (E) but does not act on the external reactant ($E_{external}$) is correlated by stoichiometric coefficients

of 1 and 0, respectively. Demand reactions such as V_{growth} can also be included in the stoichiometric matrix being correlated with substrates by an appropriate stoichiometric coefficient.

As set forth in further detail below, a stoichiometric matrix provides a convenient format for representing and analyzing a reaction network because it can be readily manipulated and used to compute network properties, for example, by using linear programming or general convex analysis. A reaction network data structure can take on a variety of formats so long as it is capable of relating reactants and reactions in the manner exemplified above for a stoichiometric matrix and in a manner that can be manipulated to determine an activity of one or more reactions using methods such as those exemplified below. Other examples of reaction network data structures that are useful in the invention include a connected graph, list of chemical reactions or a table of reaction equations.

A reaction network data structure can be constructed to include all reactions that are involved in *Homo sapiens* metabolism or any portion thereof. A portion of *Homo sapiens* metabolic reactions that can be included in a reaction network data structure of the invention includes, for example, a central metabolic pathway such as glycolysis, the TCA cycle, the PPP or ETS; or a peripheral metabolic pathway such as amino acid biosynthesis, amino acid degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, vitamin or cofactor biosynthesis, transport processes and alternative carbon source catabolism. Examples of

individual pathways within the peripheral pathways are set forth in Table 1.

Depending upon a particular application, a reaction network data structure can include a plurality of *Homo sapiens* reactions including any or all of the reactions listed in Table 1.

For some applications, it can be advantageous to use a reaction network data structure that includes a minimal number of reactions to achieve a particular *Homo sapiens* activity under a particular set of environmental conditions. A reaction network data structure having a minimal number of reactions can be identified by performing the simulation methods described below in an iterative fashion where different reactions or sets of reactions are systematically removed and the effects observed. Accordingly, the invention provides a computer readable medium, containing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein the plurality of *Homo sapiens* reactions contains at least 65 reactions. For example, the core metabolic reaction database shown in Tables 2 and 3 contains 65 reactions, and is sufficient to simulate aerobic and anaerobic metabolism on a number of carbon sources, including glucose.

Depending upon the particular cell type or types, the physiological, pathological or therapeutic conditions being tested and the desired activity, a reaction network data structure can contain smaller numbers of reactions such as at least 200, 150, 100 or 50 reactions. A reaction network data structure having relatively few reactions can provide the advantage of reducing computation time and resources required to

perform a simulation. When desired, a reaction network data structure having a particular subset of reactions can be made or used in which reactions that are not relevant to the particular simulation are omitted. Alternatively, larger numbers of reactions can be included in order to increase the accuracy or molecular detail of the methods of the invention or to suit a particular application. Thus, a reaction network data structure can contain at least 300, 350, 400, 450, 500, 550, 600 or more reactions up to the number of reactions that occur in or by *Homo sapiens* or that are desired to simulate the activity of the full set of reactions occurring in *Homo sapiens*. A reaction network data structure that is substantially complete with respect to the metabolic reactions of *Homo sapiens* provides the advantage of being relevant to a wide range of conditions to be simulated, whereas those with smaller numbers of metabolic reactions are limited to a particular subset of conditions to be simulated.

A *Homo sapiens* reaction network data structure can include one or more reactions that occur in or by *Homo sapiens* and that do not occur, either naturally or following manipulation, in or by another organism, such as *Saccharomyces cerevisiae*. It is understood that a *Homo sapiens* reaction network data structure of a particular cell type can also include one or more reactions that occur in another cell type. Addition of such heterologous reactions to a reaction network data structure of the invention can be used in methods to predict the consequences of heterologous gene transfer and protein expression, for example, when designing *in vivo* and *ex vivo* gene therapy approaches.

The reactions included in a reaction network data structure of the invention can be metabolic reactions. A reaction network data structure can also be constructed to include other types of reactions such as regulatory reactions, signal transduction reactions, cell cycle reactions, reactions controlling developmental processes, reactions involved in apoptosis, reactions involved in responses to hypoxia, reactions involved in responses to cell-cell or cell-substrate interactions, reactions involved in protein synthesis and regulation thereof, reactions involved in gene transcription and translation, and regulation thereof, and reactions involved in assembly of a cell and its subcellular components.

A reaction network data structure or index of reactions used in the data structure such as that available in a metabolic reaction database, as described above, can be annotated to include information about a particular reaction. A reaction can be annotated to indicate, for example, assignment of the reaction to a protein, macromolecule or enzyme that performs the reaction, assignment of a gene(s) that codes for the protein, macromolecule or enzyme, the Enzyme Commission (EC) number of the particular metabolic reaction, a subset of reactions to which the reaction belongs, citations to references from which information was obtained, or a level of confidence with which a reaction is believed to occur in *Homo sapiens*. A computer readable medium or media of the invention can include a gene database containing annotated reactions. Such information can be obtained during the course of building a metabolic reaction database or model of the invention as described below.

As used herein, the term "gene database" is intended to mean a computer readable medium or media that contains at least one reaction that is annotated to assign a reaction to one or more macromolecules that perform the reaction or to assign one or more nucleic acid that encodes the one or more macromolecules that perform the reaction. A gene database can contain a plurality of reactions, some or all of which are annotated. An annotation can include, for example, a name for a macromolecule; assignment of a function to a macromolecule; assignment of an organism that contains the macromolecule or produces the macromolecule; assignment of a subcellular location for the macromolecule; assignment of conditions under which a macromolecule is regulated with respect to performing a reaction, being expressed or being degraded; assignment of a cellular component that regulates a macromolecule; an amino acid or nucleotide sequence for the macromolecule; or any other annotation found for a macromolecule in a genome database such as those that can be found in Genbank, a site maintained by the NCBI (ncbi.nlm.gov), the Kyoto Encyclopedia of Genes and Genomes (KEGG) (www.genome.ad.jp/kegg/), the protein database SWISS-PROT (ca.expasy.org/sprot/), the LocusLink database maintained by the NCBI (www.ncbi.nlm.nih.gov/LocusLink/), the Enzyme Nomenclature database maintained by G.P. Moss of Queen Mary and Westfield College in the United Kingdom (www.chem.qmw.ac.uk/iubmb/enzyme/).

A gene database of the invention can include a substantially complete collection of genes or open reading frames in *Homo sapiens* or a substantially complete collection of the macromolecules encoded by the *Homo sapiens* genome. Alternatively, a gene database can include a portion of genes or open reading

frames in *Homo sapiens* or a portion of the macromolecules encoded by the *Homo sapiens* genome, such as the portion that includes substantially all metabolic genes or macromolecules. The portion can be at least 10%, 15%, 20%, 25%, 50%, 75%, 90% or 95% of the genes or open reading frames encoded by the *Homo sapiens* genome, or the macromolecules encoded therein. A gene database can also include macromolecules encoded by at least a portion of the nucleotide sequence for the *Homo sapiens* genome such as at least 10%, 15%, 20%, 25%, 50%, 75%, 90% or 95% of the *Homo sapiens* genome. Accordingly, a computer readable medium or media of the invention can include at least one reaction for each macromolecule encoded by a portion of the *Homo sapiens* genome.

An *in silico Homo sapiens* model of the invention can be built by an iterative process which includes gathering information regarding particular reactions to be added to a model, representing the reactions in a reaction network data structure, and performing preliminary simulations wherein a set of constraints is placed on the reaction network and the output evaluated to identify errors in the network. Errors in the network such as gaps that lead to non-natural accumulation or consumption of a particular metabolite can be identified as described below and simulations repeated until a desired performance of the model is attained. An exemplary method for iterative model construction is provided in Example I.

Thus, the invention provides a method for making a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions in a computer readable medium or media. The

method includes the steps of: (a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of the *Homo sapiens* reactions; (b) relating the plurality of *Homo sapiens* reactants to the plurality of *Homo sapiens* reactions in a data structure, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product; (c) making a constraint set for the plurality of *Homo sapiens* reactions; (d) providing an objective function; (e) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, and (f) if the at least one flux distribution is not predictive of *Homo sapiens* physiology, then adding a reaction to or deleting a reaction from the data structure and repeating step (e), if the at least one flux distribution is predictive of *Homo sapiens* physiology, then storing the data structure in a computer readable medium or media.

Information to be included in a data structure of the invention can be gathered from a variety of sources including, for example, annotated genome sequence information and biochemical literature.

Sources of annotated human genome sequence information include, for example, KEGG, SWISS-PROT, LocusLink, the Enzyme Nomenclature database, the International Human Genome Sequencing Consortium and commercial databases. KEGG contains a broad range of information, including a substantial amount of metabolic reconstruction. The genomes of 63 organisms

can be accessed here, with gene products grouped by coordinated functions, often represented by a map (e.g., the enzymes involved in glycolysis would be grouped together). The maps are biochemical pathway templates which show enzymes connecting metabolites for various parts of metabolism. These general pathway templates are customized for a given organism by highlighting enzymes on a given template which have been identified in the genome of the organism. Enzymes and metabolites are active and yield useful information about stoichiometry, structure, alternative names and the like, when accessed.

SWISS-PROT contains detailed information about protein function. Accessible information includes alternate gene and gene product names, function, structure and sequence information, relevant literature references, and the like.

LocusLink contains general information about the locus where the gene is located and, of relevance, tissue specificity, cellular location, and implication of the gene product in various disease states.

The Enzyme Nomenclature database can be used to compare the gene products of two organisms. Often the gene names for genes with similar functions in two or more organisms are unrelated. When this is the case, the E.C. (Enzyme Commission) numbers can be used as unambiguous indicators of gene product function. The information in the Enzyme Nomenclature database is also published in Enzyme Nomenclature (Academic Press, San Diego, California, 1992) with 5 supplements to date, all found in the European Journal of Biochemistry (Blackwell Science, Malden, MA).

Sources of biochemical information include, for example, general resources relating to metabolism, resources relating specifically to human metabolism, and resources relating to the biochemistry, physiology and pathology of specific human cell types.

Sources of general information relating to metabolism, which were used to generate the human reaction databases and models described herein, were J.G. Salway, Metabolism at a Glance, 2nd ed., Blackwell Science, Malden, MA (1999) and T.M. Devlin, ed., Textbook of Biochemistry with Clinical Correlations, 4th ed., John Wiley and Sons, New York, NY (1997). Human metabolism-specific resources included J.R. Bronk, Human Metabolism: Functional Diversity and Integration, Addison Wesley Longman, Essex, England (1999).

The literature used in conjunction with the skeletal muscle metabolic models and simulations described herein included R. Maughan et al., Biochemistry of Exercise and Training, Oxford University Press, Oxford, England (1997), as well as references on muscle pathology such as S. Carpenter et al., Pathology of Skeletal Muscle, 2nd ed., Oxford University Press, Oxford, England (2001), and more specific articles on muscle metabolism as may be found in the Journal of Physiology (Cambridge University Press, Cambridge, England).

In the course of developing an *in silico* model of *Homo sapiens* metabolism, the types of data that can be considered include, for example, biochemical information which is information related to the experimental characterization of a chemical reaction, often directly indicating a protein(s)

associated with a reaction and the stoichiometry of the reaction or indirectly demonstrating the existence of a reaction occurring within a cellular extract; genetic information, which is information related to the experimental identification and genetic characterization of a gene(s) shown to code for a particular protein(s) implicated in carrying out a biochemical event; genomic information, which is information related to the identification of an open reading frame and functional assignment, through computational sequence analysis, that is then linked to a protein performing a biochemical event; physiological information, which is information related to overall cellular physiology, fitness characteristics, substrate utilization, and phenotyping results, which provide evidence of the assimilation or dissimilation of a compound used to infer the presence of specific biochemical event (in particular translocations); and modeling information, which is information generated through the course of simulating activity of *Homo sapiens* cells using methods such as those described herein which lead to predictions regarding the status of a reaction such as whether or not the reaction is required to fulfill certain demands placed on a metabolic network. Additional information relevant to multicellular organisms that can be considered includes cell type-specific or condition-specific gene expression information, which can be determined experimentally, such as by gene array analysis or from expressed sequence tag (EST) analysis, or obtained from the biochemical and physiological literature.

The majority of the reactions occurring in *Homo sapiens* reaction networks are catalyzed by enzymes/proteins, which are created through the transcription and translation of the genes found within

the chromosome in the cell. The remaining reactions occur either spontaneously or through non-enzymatic processes. Furthermore, a reaction network data structure can contain reactions that add or delete steps to or from a particular reaction pathway. For example, reactions can be added to optimize or improve performance of a *Homo sapiens* model in view of empirically observed activity. Alternatively, reactions can be deleted to remove intermediate steps in a pathway when the intermediate steps are not necessary to model flux through the pathway. For example, if a pathway contains 3 nonbranched steps, the reactions can be combined or added together to give a net reaction, thereby reducing memory required to store the reaction network data structure and the computational resources required for manipulation of the data structure.

The reactions that occur due to the activity of gene-encoded enzymes can be obtained from a genome database which lists genes identified from genome sequencing and subsequent genome annotation. Genome annotation consists of the locations of open reading frames and assignment of function from homology to other known genes or empirically determined activity. Such a genome database can be acquired through public or private databases containing annotated *Homo sapiens* nucleic acid or protein sequences. If desired, a model developer can perform a network reconstruction and establish the model content associations between the genes, proteins, and reactions as described, for example, in Covert et al. Trends in Biochemical Sciences 26:179-186 (2001) and Palsson, WO 00/46405.

As reactions are added to a reaction network data structure or metabolic reaction database, those

having known or putative associations to the proteins/enzymes which enable/catalyze the reaction and the associated genes that code for these proteins can be identified by annotation. Accordingly, the appropriate associations for all of the reactions to their related proteins or genes or both can be assigned. These associations can be used to capture the non-linear relationship between the genes and proteins as well as between proteins and reactions. In some cases one gene codes for one protein which then perform one reaction. However, often there are multiple genes which are required to create an active enzyme complex and often there are multiple reactions that can be carried out by one protein or multiple proteins that can carry out the same reaction. These associations capture the logic (i.e. AND or OR relationships) within the associations. Annotating a metabolic reaction database with these associations can allow the methods to be used to determine the effects of adding or eliminating a particular reaction not only at the reaction level, but at the genetic or protein level in the context of running a simulation or predicting *Homo sapiens* activity.

A reaction network data structure of the invention can be used to determine the activity of one or more reactions in a plurality of *Homo sapiens* reactions independent of any knowledge or annotation of the identity of the protein that performs the reaction or the gene encoding the protein. A model that is annotated with gene or protein identities can include reactions for which a protein or encoding gene is not assigned. While a large portion of the reactions in a cellular metabolic network are associated with genes in the organism's genome, there are also a substantial number of reactions included in a model for which there

are no known genetic associations. Such reactions can be added to a reaction database based upon other information that is not necessarily related to genetics such as biochemical or cell based measurements or theoretical considerations based on observed biochemical or cellular activity. For example, there are many reactions that can either occur spontaneously or are not protein-enabled reactions. Furthermore, the occurrence of a particular reaction in a cell for which no associated proteins or genetics have been currently identified can be indicated during the course of model building by the iterative model building methods of the invention.

The reactions in a reaction network data structure or reaction database can be assigned to subsystems by annotation, if desired. The reactions can be subdivided according to biological criteria, such as according to traditionally identified metabolic pathways (glycolysis, amino acid metabolism and the like) or according to mathematical or computational criteria that facilitate manipulation of a model that incorporates or manipulates the reactions. Methods and criteria for subdviding a reaction database are described in further detail in Schilling et al., J. Theor. Biol. 203:249-283 (2000), and in Schuster et al., Bioinformatics 18:351-361 (2002). The use of subsystems can be advantageous for a number of analysis methods, such as extreme pathway analysis, and can make the management of model content easier. Although assigning reactions to subsystems can be achieved without affecting the use of the entire model for simulation, assigning reactions to subsystems can allow a user to search for reactions in a particular subsystem which may be useful in performing various types of analyses. Therefore, a reaction network data

structure can include any number of desired subsystems including, for example, 2 or more subsystems, 5 or more subsystems, 10 or more subsystems, 25 or more subsystems or 50 or more subsystems.

The reactions in a reaction network data structure or metabolic reaction database can be annotated with a value indicating the confidence with which the reaction is believed to occur in the *Homo sapiens* cell. The level of confidence can be, for example, a function of the amount and form of supporting data that is available. This data can come in various forms including published literature, documented experimental results, or results of computational analyses. Furthermore, the data can provide direct or indirect evidence for the existence of a chemical reaction in a cell based on genetic, biochemical, and/or physiological data.

The invention further provides a computer readable medium, containing (a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, and (b) a constraint set for the plurality of *Homo sapiens* reactions.

Constraints can be placed on the value of any of the fluxes in the metabolic network using a constraint set. These constraints can be representative of a minimum or maximum allowable flux through a given reaction, possibly resulting from a limited amount of an enzyme present. Additionally, the

constraints can determine the direction or reversibility of any of the reactions or transport fluxes in the reaction network data structure. Based on the *in vivo* environment where *Homo sapiens* lives the metabolic resources available to the cell for biosynthesis of essential molecules for can be determined. Allowing the corresponding transport fluxes to be active provides the *in silico Homo sapiens* with inputs and outputs for substrates and by-products produced by the metabolic network.

Returning to the hypothetical reaction network shown in Figure 1, constraints can be placed on each reaction in the exemplary format shown in Figure 2, as follows. The constraints are provided in a format that can be used to constrain the reactions of the stoichiometric matrix shown in Figure 3. The format for the constraints used for a matrix or in linear programming can be conveniently represented as a linear inequality such as

$$b_j \leq v_j \leq a_j : j = 1....n \qquad \text{(Eq. 1)}$$

where v_j is the metabolic flux vector, b_j is the minimum flux value and a_j is the maximum flux value. Thus, a_j can take on a finite value representing a maximum allowable flux through a given reaction or b_j can take on a finite value representing minimum allowable flux through a given reaction. Additionally, if one chooses to leave certain reversible reactions or transport fluxes to operate in a forward and reverse manner the flux may remain unconstrained by setting b_j to negative infinity and a_j to positive infinity as shown for reaction R_2 in Figure 2. If reactions proceed only in the forward reaction b_j is set to zero while a_j is set to positive infinity as shown for

reactions R_1, R_3, R_4, R_5, and R_6 in Figure 2. As an example, to simulate the event of a genetic deletion or non-expression of a particular protein, the flux through all of the corresponding metabolic reactions related to the gene or protein in question are reduced to zero by setting a_j and b_j to be zero. Furthermore, if one wishes to simulate the absence of a particular growth substrate one can simply constrain the corresponding transport fluxes that allow the metabolite to enter the cell to be zero by setting a_j and b_j to be zero. On the other hand if a substrate is only allowed to enter or exit the cell via transport mechanisms, the corresponding fluxes can be properly constrained to reflect this scenario.

The ability of a reaction to be actively occurring is dependent on a large number of additional factors beyond just the availability of substrates. These factors, which can be represented as variable constraints in the models and methods of the invention include, for example, the presence of cofactors necessary to stabilize the protein/enzyme, the presence or absence of enzymatic inhibition and activation factors, the active formation of the protein/enzyme through translation of the corresponding mRNA transcript, the transcription of the associated gene(s) or the presence of chemical signals and/or proteins that assist in controlling these processes that ultimately determine whether a chemical reaction is capable of being carried out within an organism. Of particular importance in the regulation of human cell types is the implementation of paracrine and endocrine signaling pathways to control cellular activities. In these cases a cell secretes signaling molecules that may be carried far afield to act on distant targets (endocrine signaling), or act as local mediators

(paracrine signaling). Examples of endocrine signaling molecules include hormones such as insulin, while examples of paracrine signaling molecules include neurotransmitters such as acetylcholine. These molecules induce cellular responses through signaling cascades that affect the activity of biochemical reactions in the cell. Regulation can be represented in an *in silico Homo sapiens* model by providing a variable constraint as set forth below.

Thus, the invention provides a computer readable medium or media, including (a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, and wherein at least one of the reactions is a regulated reaction; and (b) a constraint set for the plurality of reactions, wherein the constraint set includes a variable constraint for the regulated reaction.

As used herein, the term "regulated," when used in reference to a reaction in a data structure, is intended to mean a reaction that experiences an altered flux due to a change in the value of a constraint or a reaction that has a variable constraint.

As used herein, the term "regulatory reaction" is intended to mean a chemical conversion or interaction that alters the activity of a protein, macromolecule or enzyme. A chemical conversion or interaction can directly alter the activity of a protein, macromolecule or enzyme such as occurs when

the protein, macromolecule or enzyme is post-translationally modified or can indirectly alter the activity of a protein, macromolecule or enzyme such as occurs when a chemical conversion or binding event leads to altered expression of the protein, macromolecule or enzyme. Thus, transcriptional or translational regulatory pathways can indirectly alter a protein, macromolecule or enzyme or an associated reaction. Similarly, indirect regulatory reactions can include reactions that occur due to downstream components or participants in a regulatory reaction network. When used in reference to a data structure or *in silico Homo sapiens* model, the term is intended to mean a first reaction that is related to a second reaction by a function that alters the flux through the second reaction by changing the value of a constraint on the second reaction.

As used herein, the term "regulatory data structure" is intended to mean a representation of an event, reaction or network of reactions that activate or inhibit a reaction, the representation being in a format that can be manipulated or analyzed. An event that activates a reaction can be an event that initiates the reaction or an event that increases the rate or level of activity for the reaction. An event that inhibits a reaction can be an event that stops the reaction or an event that decreases the rate or level of activity for the reaction. Reactions that can be represented in a regulatory data structure include, for example, reactions that control expression of a macromolecule that in turn, performs a reaction such as transcription and translation reactions, reactions that lead to post translational modification of a protein or enzyme such as phophorylation, dephosphorylation, prenylation, methylation, oxidation or covalent

modification, reactions that process a protein or enzyme such as removal of a pre- or pro-sequence, reactions that degrade a protein or enzyme or reactions that lead to assembly of a protein or enzyme.

As used herein, the term "regulatory event" is intended to mean a modifier of the flux through a reaction that is independent of the amount of reactants available to the reaction. A modification included in the term can be a change in the presence, absence, or amount of an enzyme that performs a reaction. A modifier included in the term can be a regulatory reaction such as a signal transduction reaction or an environmental condition such as a change in pH, temperature, redox potential or time. It will be understood that when used in reference to an *in silico Homo sapiens* model or data structure a regulatory event is intended to be a representation of a modifier of the flux through a *Homo sapiens* reaction that is independent of the amount of reactants available to the reaction.

The effects of regulation on one or more reactions that occur in *Homo sapiens* can be predicted using an *in silico Homo sapiens* model of the invention. Regulation can be taken into consideration in the context of a particular condition being examined by providing a variable constraint for the reaction in an *in silico Homo sapiens* model. Such constraints constitute condition-dependent constraints. A data structure can represent regulatory reactions as Boolean logic statements (Reg-reaction). The variable takes on a value of 1 when the reaction is available for use in the reaction network and will take on a value of 0 if the reaction is restrained due to some regulatory feature. A series of Boolean statements can then be

introduced to mathematically represent the regulatory network as described for example in Covert et al. J. Theor. Biol. 213:73-88 (2001). For example, in the case of a transport reaction (A_in) that imports metabolite A, where metabolite A inhibits reaction R2 as shown in Figure 4, a Boolean rule can state that:

Reg-R2 = IF NOT(A_in). (Eq. 2)

This statement indicates that reaction R2 can occur if reaction A_in is not occurring (i.e. if metabolite A is not present). Similarly, it is possible to assign the regulation to a variable A which would indicate an amount of A above or below a threshold that leads to the inhibition of reaction R2. Any function that provides values for variables corresponding to each of the reactions in the biochemical reaction network can be used to represent a regulatory reaction or set of regulatory reactions in a regulatory data structure. Such functions can include, for example, fuzzy logic, heuristic rule-based descriptions, differential equations or kinetic equations detailing system dynamics.

A reaction constraint placed on a reaction can be incorporated into an *in silico Homo sapiens* model using the following general equation:

$$(\text{Reg-Reaction})*b_j \le v_j \le a_j*(\text{Reg-Reaction}) \quad :(\text{Eq. 3})$$

$$j = 1....n$$

For the example of reaction R2 this equation is written as follows:

$$(0)*\text{Reg-R2} \le \text{R2} \le (\infty)*\text{Reg-R2}. \qquad (\text{Eq. 4})$$

Thus, during the course of a simulation, depending upon the presence or absence of metabolite A in the interior of the cell where reaction R2 occurs, the value for the upper boundary of flux for reaction R2 will change from 0 to infinity, respectively.

With the effects of a regulatory event or network taken into consideration by a constraint function and the condition-dependent constraints set to an initial relevant value, the behavior of the *Homo sapiens* reaction network can be simulated for the conditions considered as set forth below.

Although regulation has been exemplified above for the case where a variable constraint is dependent upon the outcome of a reaction in the data structure, a plurality of variable constraints can be included in an *in silico Homo sapiens* model to represent regulation of a plurality of reactions. Furthermore, in the exemplary case set forth above, the regulatory structure includes a general control stating that a reaction is inhibited by a particular environmental condition. Using a general control of this type, it is possible to incorporate molecular mechanisms and additional detail into the regulatory structure that is responsible for determining the active nature of a particular chemical reaction within an organism.

Regulation can also be simulated by a model of the invention and used to predict a *Homo sapiens* physiological function without knowledge of the precise molecular mechanisms involved in the reaction network being modeled. Thus, the model can be used to predict, *in silico*, overall regulatory events or causal relationships that are not apparent from *in vivo*

observation of any one reaction in a network or whose *in vivo* effects on a particular reaction are not known. Such overall regulatory effects can include those that result from overall environmental conditions such as changes in pH, temperature, redox potential, or the passage of time.

The *in silico Homo sapiens* model and methods described herein can be implemented on any conventional host computer system, such as those based on Intel.RTM. microprocessors and running Microsoft Windows operating systems. Other systems, such as those using the UNIX or LINUX operating system and based on IBM.RTM., DEC.RTM. or Motorola.RTM. microprocessors are also contemplated. The systems and methods described herein can also be implemented to run on client-server systems and wide-area networks, such as the Internet.

Software to implement a method or model of the invention can be written in any well-known computer language, such as Java, C, C++, Visual Basic, FORTRAN or COBOL and compiled using any well-known compatible compiler. The software of the invention normally runs from instructions stored in a memory on a host computer system. A memory or computer readable medium can be a hard disk, floppy disc, compact disc, magneto-optical disc, Random Access Memory, Read Only Memory or Flash Memory. The memory or computer readable medium used in the invention can be contained within a single computer or distributed in a network. A network can be any of a number of conventional network systems known in the art such as a local area network (LAN) or a wide area network (WAN). Client-server environments, database servers and networks that can be used in the invention are well known in the art. For example, the database server can run on an operating system such as UNIX,

running a relational database management system, a World Wide Web application and a World Wide Web server. Other types of memories and computer readable media are also contemplated to function within the scope of the invention.

A database or data structure of the invention can be represented in a markup language format including, for example, Standard Generalized Markup Language (SGML), Hypertext markup language (HTML) or Extensible Markup language (XML). Markup languages can be used to tag the information stored in a database or data structure of the invention, thereby providing convenient annotation and transfer of data between databases and data structures. In particular, an XML format can be useful for structuring the data representation of reactions, reactants and their annotations; for exchanging database contents, for example, over a network or internet; for updating individual elements using the document object model; or for providing differential access to multiple users for different information content of a data base or data structure of the invention. XML programming methods and editors for writing XML code are known in the art as described, for example, in Ray, "Learning XML" O'Reilly and Associates, Sebastopol, CA (2001).

A set of constraints can be applied to a reaction network data structure to simulate the flux of mass through the reaction network under a particular set of environmental conditions specified by a constraints set. Because the time constants characterizing metabolic transients and/or metabolic reactions are typically very rapid, on the order of milli-seconds to seconds, compared to the time constants of cell growth on the order of hours to days,

the transient mass balances can be simplified to only consider the steady state behavior. Referring now to an example where the reaction network data structure is a stoichiometric matrix, the steady state mass balances can be applied using the following system of linear equations

$$S \bullet v = 0 \qquad \text{(Eq. 5)}$$

where S is the stoichiometric matrix as defined above and v is the flux vector. This equation defines the mass, energy, and redox potential constraints placed on the metabolic network as a result of stoichiometry. Together Equations 1 and 5 representing the reaction constraints and mass balances, respectively, effectively define the capabilities and constraints of the metabolic genotype and the organism's metabolic potential. All vectors, v, that satisfy Equation 5 are said to occur in the mathematical nullspace of S. Thus, the null space defines steady-state metabolic flux distributions that do not violate the mass, energy, or redox balance constraints. Typically, the number of fluxes is greater than the number of mass balance constraints, thus a plurality of flux distributions satisfy the mass balance constraints and occupy the null space. The null space, which defines the feasible set of metabolic flux distributions, is further reduced in size by applying the reaction constraints set forth in Equation 1 leading to a defined solution space. A point in this space represents a flux distribution and hence a metabolic phenotype for the network. An optimal solution within the set of all solutions can be determined using mathematical optimization methods when provided with a stated objective and a constraint set. The calculation of any solution constitutes a simulation of the model.

Objectives for activity of a human cell can be chosen. While the overall objective of a multi-cellular organism may be growth or reproduction, individual human cell types generally have much more complex objectives, even to the seemingly extreme objective of apoptosis (programmed cell death), which may benefit the organism but certainly not the individual cell. For example, certain cell types may have the objective of maximizing energy production, while others have the objective of maximizing the production of a particular hormone, extracellular matrix component, or a mechanical property such as contractile force. In cases where cell reproduction is slow, such as human skeletal muscle, growth and its effects need not be taken into account. In other cases, biomass composition and growth rate could be incorporated into a "maintenance" type of flux, where rather than optimizing for growth, production of precursors is set at a level consistent with experimental knowledge and a different objective is optimized.

Certain cell types, including cancer cells, can be viewed as having an objective of maximizing cell growth. Growth can be defined in terms of biosynthetic requirements based on literature values of biomass composition or experimentally determined values such as those obtained as described above. Thus, biomass generation can be defined as an exchange reaction that removes intermediate metabolites in the appropriate ratios and represented as an objective function. In addition to draining intermediate metabolites this reaction flux can be formed to utilize energy molecules such as ATP, NADH and NADPH so as to incorporate any maintenance requirement that must be met. This new reaction flux then becomes another constraint/balance

equation that the system must satisfy as the objective function. Using the stoichiometric matrix of Figure 3 as an example, adding such a constraint is analogous to adding the additional column V_{growth} to the stoichiometric matrix to represent fluxes to describe the production demands placed on the metabolic system. Setting this new flux as the objective function and asking the system to maximize the value of this flux for a given set of constraints on all the other fluxes is then a method to simulate the growth of the organism.

Continuing with the example of the stoichiometric matrix applying a constraint set to a reaction network data structure can be illustrated as follows. The solution to equation 5 can be formulated as an optimization problem, in which the flux distribution that minimizes a particular objective is found. Mathematically, this optimization problem can be stated as:

$$\text{Minimize } Z \qquad \text{(Eq. 6)}$$

$$\text{where } z = \sum c_i \cdot v_i \qquad \text{(Eq. 7)}$$

where Z is the objective which is represented as a linear combination of metabolic fluxes v_i using the weights c_i in this linear combination. The optimization problem can also be stated as the equivalent maximization problem; i.e. by changing the sign on Z. Any commands for solving the optimazation problem can be used including, for example, linear programming commands.

A computer system of the invention can further include a user interface capable of receiving a representation of one or more reactions. A user interface of the invention can also be capable of sending at least one command for modifying the data structure, the constraint set or the commands for applying the constraint set to the data representation, or a combination thereof. The interface can be a graphic user interface having graphical means for making selections such as menus or dialog boxes. The interface can be arranged with layered screens accessible by making selections from a main screen. The user interface can provide access to other databases useful in the invention such as a metabolic reaction database or links to other databases having information relevant to the reactions or reactants in the reaction network data structure or to *Homo sapiens* physiology. Also, the user interface can display a graphical representation of a reaction network or the results of a simulation using a model of the invention.

Once an initial reaction network data structure and set of constraints has been created, this model can be tested by preliminary simulation. During preliminary simulation, gaps in the network or "dead-ends" in which a metabolite can be produced but not consumed or where a metabolite can be consumed but not produced can be identified. Based on the results of preliminary simulations areas of the metabolic reconstruction that require an additional reaction can be identified. The determination of these gaps can be readily calculated through appropriate queries of the reaction network data structure and need not require the use of simulation strategies, however, simulation would be an alternative approach to locating such gaps.

In the preliminary simulation testing and model content refinement stage the existing model is subjected to a series of functional tests to determine if it can perform basic requirements such as the ability to produce the required biomass constituents and generate predictions concerning the basic physiological characteristics of the particular cell type being modeled. The more preliminary testing that is conducted the higher the quality of the model that will be generated. Typically, the majority of the simulations used in this stage of development will be single optimizations. A single optimization can be used to calculate a single flux distribution demonstrating how metabolic resources are routed determined from the solution to one optimization problem. An optimization problem can be solved using linear programming as demonstrated in the Examples below. The result can be viewed as a display of a flux distribution on a reaction map. Temporary reactions can be added to the network to determine if they should be included into the model based on modeling/simulation requirements.

Once a model of the invention is sufficiently complete with respect to the content of the reaction network data structure according to the criteria set forth above, the model can be used to simulate activity of one or more reactions in a reaction network. The results of a simulation can be displayed in a variety of formats including, for example, a table, graph, reaction network, flux distribution map or a phenotypic phase plane graph.

Thus, the invention provides a method for predicting a *Homo sapiens* physiological function. The method includes the steps of (a) providing a data

structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product; (b) providing a constraint set for the plurality of *Homo sapiens* reactions; (c) providing an objective function, and (d) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function.

A method for predicting a *Homo sapiens* physiological function can include the steps of (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, and wherein at least one of the reactions is a regulated reaction; (b) providing a constraint set for the plurality of reactions, wherein the constraint set includes a variable constraint for the regulated reaction; (c) providing a condition-dependent value to the variable constraint; (d) providing an objective function, and (e) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function.

As used herein, the term "physiological function," when used in reference to *Homo sapiens*, is intended to mean an activity of a *Homo sapiens* cell as a whole. An activity included in the term can be the magnitude or rate of a change from an initial state of a *Homo sapiens* cell to a final state of the *Homo sapiens* cell. An activity included in the term can be, for example, growth, energy production, redox equivalent production, biomass production, development, or consumption of carbon nitrogen, sulfur, phosphate, hydrogen or oxygen. An activity can also be an output of a particular reaction that is determined or predicted in the context of substantially all of the reactions that affect the particular reaction in a *Homo sapiens* cell or substantially all of the reactions that occur in a *Homo sapiens* cell (e.g. muscle contraction). Examples of a particular reaction included in the term are production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor or transport of a metabolite. A physiological function can include an emergent property which emerges from the whole but not from the sum of parts where the parts are observed in isolation (see for example, Palsson, <u>Nat. Biotech</u> 18:1147-1150 (2000)).

A physiological function of *Homo sapiens* reactions can be determined using phase plane analysis of flux distributions. Phase planes are representations of the feasible set which can be presented in two or three dimensions. As an example, two parameters that describe the growth conditions such as substrate and oxygen uptake rates can be defined as two axes of a two-dimensional space. The optimal flux

distribution can be calculated from a reaction network data structure and a set of constraints as set forth above for all points in this plane by repeatedly solving the linear programming problem while adjusting the exchange fluxes defining the two-dimensional space. A finite number of qualitatively different metabolic pathway utilization patterns can be identified in such a plane, and lines can be drawn to demarcate these regions. The demarcations defining the regions can be determined using shadow prices of linear optimization as described, for example in Chvatal, Linear Programming New York, W.H. Freeman and Co. (1983). The regions are referred to as regions of constant shadow price structure. The shadow prices define the intrinsic value of each reactant toward the objective function as a number that is either negative, zero, or positive and are graphed according to the uptake rates represented by the x and y axes. When the shadow prices become zero as the value of the uptake rates are changed there is a qualitative shift in the optimal reaction network.

One demarcation line in the phenotype phase plane is defined as the line of optimality (LO). This line represents the optimal relation between respective metabolic fluxes. The LO can be identified by varying the x-axis flux and calculating the optimal y-axis flux with the objective function defined as the growth flux . From the phenotype phase plane analysis the conditions under which a desired activity is optimal can be determined. The maximal uptake rates lead to the definition of a finite area of the plot that is the predicted outcome of a reaction network within the environmental conditions represented by the constraint set. Similar analyses can be performed in multiple dimensions where each dimension on the plot corresponds

to a different uptake rate. These and other methods for using phase plane analysis, such as those described in Edwards et al., Biotech Bioeng. 77:27-36(2002), can be used to analyze the results of a simulation using an *in silico Homo sapiens* model of the invention.

A physiological function of *Homo sapiens* can also be determined using a reaction map to display a flux distribution. A reaction map of *Homo sapiens* can be used to view reaction networks at a variety of levels. In the case of a cellular metabolic reaction network a reaction map can contain the entire reaction complement representing a global perspective. Alternatively, a reaction map can focus on a particular region of metabolism such as a region corresponding to a reaction subsystem described above or even on an individual pathway or reaction.

Thus, the invention provides an apparatus that produces a representation of a *Homo sapiens* physiological function, wherein the representation is produced by a process including the steps of: (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product; (b) providing a constraint set for the plurality of *Homo sapiens* reactions; (c) providing an objective function; (d) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function, and (e) producing

a representation of the activity of the one or more *Homo sapiens* reactions.

The methods of the invention can be used to determine the activity of a plurality of *Homo sapiens* reactions including, for example, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, transport of a metabolite and metabolism of an alternative carbon source. In addition, the methods can be used to determine the activity of one or more of the reactions described above or listed in Table 1.

The methods of the invention can be used to determine a phenotype of a *Homo sapiens* mutant. The activity of one or more *Homo sapiens* reactions can be determined using the methods described above, wherein the reaction network data structure lacks one or more gene-associated reactions that occur in *Homo sapiens*. Alternatively, the methods can be used to determine the activity of one or more *Homo sapiens* reactions when a reaction that does not naturally occur in *Homo sapiens* is added to the reaction network data structure. Deletion of a gene can also be represented in a model of the invention by constraining the flux through the reaction to zero, thereby allowing the reaction to remain within the data structure. Thus, simulations can be made to predict the effects of adding or removing genes to or from *Homo sapiens*. The methods can be particularly useful for determining the effects of adding or deleting a gene that encodes for a gene product that performs a reaction in a peripheral metabolic pathway.

A drug target or target for any other agent that affects *Homo sapiens* function can be predicted using the methods of the invention. Such predictions can be made by removing a reaction to simulate total inhibition or prevention by a drug or agent. Alternatively, partial inhibition or reduction in the activity a particular reaction can be predicted by performing the methods with altered constraints. For example, reduced activity can be introduced into a model of the invention by altering the a_j or b_j values for the metabolic flux vector of a target reaction to reflect a finite maximum or minimum flux value corresponding to the level of inhibition. Similarly, the effects of activating a reaction, by initiating or increasing the activity of the reaction, can be predicted by performing the methods with a reaction network data structure lacking a particular reaction or by altering the a_j or b_j values for the metabolic flux vector of a target reaction to reflect a maximum or minimum flux value corresponding to the level of activation. The methods can be particularly useful for identifying a target in a peripheral metabolic pathway.

Once a reaction has been identified for which activation or inhibition produces a desired effect on *Homo sapiens* function, an enzyme or macromolecule that performs the reaction in *Homo sapiens* or a gene that expresses the enzyme or macromolecule can be identified as a target for a drug or other agent. A candidate compound for a target identified by the methods of the invention can be isolated or synthesized using known methods. Such methods for isolating or synthesizing compounds can include, for example, rational design based on known properties of the target (see, for example, DeCamp et al., <u>Protein Engineering Principles and Practice</u>, Ed. Cleland and Craik, Wiley-Liss, New

York, pp. 467-506 (1996)), screening the target against combinatorial libraries of compounds (see for example, Houghten *et al.*, Nature, 354, 84-86 (1991); Dooley et *al.*, Science, 266, 2019-2022 (1994), which describe an iterative approach, or R. Houghten et al. PCT/US91/08694 and U.S. Patent 5,556,762 which describe the positional-scanning approach), or a combination of both to obtain focused libraries. Those skilled in the art will know or will be able to routinely determine assay conditions to be used in a screen based on properties of the target or activity assays known in the art.

A candidate drug or agent, whether identified by the methods described above or by other methods known in the art, can be validated using an *in silico Homo sapiens* model or method of the invention. The effect of a candidate drug or agent on *Homo sapiens* physiological function can be predicted based on the activity for a target in the presence of the candidate drug or agent measured *in vitro* or *in vivo*. This activity can be represented in an *in silico Homo sapiens* model by adding a reaction to the model, removing a reaction from the model or adjusting a constraint for a reaction in the model to reflect the measured effect of the candidate drug or agent on the activity of the reaction. By running a simulation under these conditions the holistic effect of the candidate drug or agent on *Homo sapiens* physiological function can be predicted.

The methods of the invention can be used to determine the effects of one or more environmental components or conditions on an activity of a *Homo sapiens* cell. As set forth above an exchange reaction

can be added to a reaction network data structure corresponding to uptake of an environmental component, release of a component to the environment, or other environmental demand. The effect of the environmental component or condition can be further investigated by running simulations with adjusted a_j or b_j values for the metabolic flux vector of the exchange reaction target reaction to reflect a finite maximum or minimum flux value corresponding to the effect of the environmental component or condition. The environmental component can be, for example an alternative carbon source or a metabolite that when added to the environment of a *Homo sapiens* cell can be taken up and metabolized. The environmental component can also be a combination of components present for example in a minimal medium composition. Thus, the methods can be used to determine an optimal or minimal medium composition that is capable of supporting a particular activity of *Homo sapiens*.

The invention further provides a method for determining a set of environmental components to achieve a desired activity for *Homo sapiens*. The method includes the steps of (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product; (b)providing a constraint set for the plurality of *Homo sapiens* reactions; (c) applying the constraint set to the data representation, thereby determining the activity of one or more *Homo sapiens* reactions (d) determining the activity of one or more

Homo sapiens reactions according to steps (a) through (c), wherein the constraint set includes an upper or lower bound on the amount of an environmental component and (e) repeating steps (a) through (c) with a changed constraint set, wherein the activity determined in step (e) is improved compared to the activity determined in step (d).

The following examples are intended to illustrate but not limit the present invention.

EXAMPLE I

This example shows the construction of a universal *Homo sapiens* metabolic reaction database, a *Homo sapiens* core metabolic reaction database and a *Homo sapiens* muscle cell metabolic reaction database. This example also shows the iterative model building process used to generate a *Homo sapiens* core metabolic model and a *Homo sapiens* muscle cell metabolic model.

A universal *Homo sapiens* reaction database was prepared from the genome databases and biochemical literature. The reaction database shown in Table 1 contains the following information:

Locus ID - the locus number of the gene found in the LocusLink website.

Gene Ab. - various abbreviations which are used for the gene.

Reaction Stoichiometry - includes all metabolites and direction of the reaction, as well as reversibility.

E.C. - The Enzyme Commission number.

Additional information included in the universal reaction database, although not shown in Table 1, included the chapter of Salway, supra (1999), where relevant reactions were found; the cellular location, if the reaction primarily occurs in a given compartment; the SWISS PROT identifier, which can be used to locate the gene record in SWISS PROT; the full name of the gene at the given locus; the chromosomal location of the gene; the Mendelian Inheritance in Man (MIM) data associated with the gene; and the tissue type, if the gene is primarily expressed in a certain tissue. Overall, 1130 metabolic enzyme- or transporter-encoding genes were included in the universal reaction database.

Fifty-nine reactions in the universal reaction database were identified and included based on biological data as found in Salway supra (1999), currently without genome annotation. Ten additional reactions, not described in the biochemical literature or genome annotation, were subsequently included in the reaction database following preliminary simulation testing and model content refinement. These 69 reactions are shown at the end of Table 1.

From the universal *Homo sapiens* reaction database shown in Table 1, a core metabolic reaction database was established, which included core metabolic reactions as well as some amino acid and fatty acid metabolic reactions, as described in Chapters 1, 3, 4, 7, 9, 10, 13, 17, 18 and 44 of J.G. Salway, Metabolism at a Glance, 2nd ed., Blackwell Science, Malden, MA (1999). The core metabolic reaction database included 211 unique reactions, accounting for 737 genes in the *Homo sapiens* genome. The core metabolic reaction database was used, although not in its entirety, to

create the core metabolic model described in Example II.

To allow for the modeling of muscle cells, the core reaction database was expanded to include 446 unique reactions, accounting for 889 genes in the *Homo sapiens* genome. This skeletal muscle metabolic reaction database was used to create the skeletal muscle metabolic model described in Example II.

Once the core and muscle cell metabolic reaction databases were compiled, the reactions were represented as a metabolic network data structure, or "stoichiometric input file." For example, the core metabolic network data structure shown in Table 2 contains 33 reversible reactions, 31 non-reversible reactions, 97 matrix columns and 52 unique enzymes. Each reaction in Table 2 is represented so as to indicate the substrate or substrates (a negative number) and the product or products (a positive number); the stoichiometry; the name of each reaction (the term following the zero); and whether the reaction is reversible (an R following the reaction name). A metabolite that appears in the mitochondria is indicated by an "m," and a metabolite that appears in the extracellular space is indicated by an "ex."

To perform a preliminary simulation or to simulate a physiological condition, a set of inputs and outputs has to be defined and the network objective function specified. To calculate the maximum ATP production of the *Homo sapiens* core metabolic network using glucose as a carbon source, a non-zero uptake value for glucose was assigned and ATP production was maximized as the objective function, using the

representation shown in Table 2. The network's performance was examined by optimizing for the given objective function and the set of constraints defined in the input file, using flux balance analysis methods. The model was refined in an iterative manner by examining the results of the simulation and implementing the appropriate changes.

Using this iterative procedure, two metabolic reaction networks were generated, representing human core metabolism and human skeletal muscle cell metabolism.

EXAMPLE II

This example shows how human metabolism can be accurately simulated using a *Homo sapiens* core metabolic model.

The human core metabolic reaction database shown in Table 3 was used in simulations of human core metabolism. This reaction database contains a total of 65 reactions, covering the classic biochemical pathways of glycolysis, the pentose phosphate pathway, the tricitric acid cycle, oxidative phosphorylation, glycogen storage, the malate/aspartate shuttle, the glycerol phosphate shuttle, and plasma and mitochondrial membrane transporters. The reaction network was divided into three compartments: the cytosol, mitochondria, and the extracellular space. The total number of metabolites in the network is 50, of which 35 also appear in the mitochondria. This core metabolic network accounts for 250 human genes.

To perform simulations using the core metabolic network, network properties such as the P/O ratio were specified using Salway, supra (1999) as a reference. Oxidation of NADH through the Electron Transport System (ETS) was set to generate 2.5 ATP molecules (i.e. a P/O ratio of 2.5 for NADH), and that of $FADH_2$ was set to 1.5 ATP molecules (i.e. a P/O ratio of 1.5 for $FADH_2$).

Using the core metabolic network, aerobic and anaerobic metabolisms were simulated *in silico*. Secretion of metabolic by-products was in agreement with the known physiological parameters. Maximum yield of all 12 precursor-metabolites (glucose-6-phosphate, fructose-6-phosphate, ribose-5-phosphate, erythrose-4-phosphate, triose phosphate, 3-phosphoglycerate, phosphoenolpyruvate, pyruvate, acetyl CoA, α-ketoglutarate, succinyl CoA, and oxaloacetate) was examined and none found to exceed the values of its theoretical yield.

Maximum ATP yield was also examined in the cytosol and mitochondria. Salway, supra (1999) reports that in the absence of membrane proton-coupled transport systems, the energy yield is 38 ATP molecules per molecule of glucose and otherwise 31 ATP molecules per molecule of glucose. The core metabolic model demonstrated the same values as described by Salway supra (1999). Energy yield in the mitochondria was determined to be 38 molecules of ATP per glucose molecule. This is equivalent to production of energy in the absence of proton-couple transporters across mitochondrial membrane since all the protons were utilized only in oxidative phosphorylation. In the cytosol, energy yield was calculated to be 30.5 molecules of ATP per glucose molecule. This value

reflects the cost of metabolite exchange across the mitochondrial membrane as described by Salway, <u>supra</u> (1999).

EXAMPLE III

This example shows how human muscle cell metabolism can be accurately simulated under various physiological and pathological conditions using a *Homo sapiens* muscle cell metabolic model.

As described in Example I, the core metabolic model was extended to also include all the major reactions occurring in the skeletal muscle cell, adding new functions to the classical metabolic pathways found in the core model, such as fatty acid synthesis and β-oxidation, triacylglycerol and phospholipid formation, and amino acid metabolism. Simulations were performed using the muscle cell reaction database shown in Table 4. The biochemical reactions were again compartmentalized into cytosolic and mitochondrial compartments.

To simulate physiological behavior of human skeletal muscle cells, an objective function had to be defined. Growth of muscle cells occurs in time scales of several hours to days. The time scale of interest in the simulation, however, was in the order of several to tens of minutes, reflecting the time period of metabolic changes during exercise. Thus, contraction (defined as, and related to energy production) was chosen to be the objective function, and no additional constraints were imposed to represent growth demands in the cell.

To study and test the behavior of the network, twelve physiological cases (Table 5) and five disease cases (Table 6) were examined. The input and output of metabolites were specified as indicated in Table 5, and maximum energy production and metabolite secretions were calculated and taken into account.

Table 5

Metabolite Exchange	1	2	3	4	5	6	7	8	9	10	11	12
Glucose	I	I	-	-	I	I	-	-	-	-	-	-
O2	I	-	I	-	I	-	I	-	I	-	I	-
Palmitate	I	I	-	-	-	-	-	-	I	I	-	-
Glycogen	I	I	I	I	-	-	-	-	-	-	-	-
Phosphocrea-tine	I	I	-	-	-	-	-	-	-	-	I	I
Triacylgly-cerol	I	I	-	-	-	-	I	I	-	-	-	-
Isoleucine	I	I	-	-	-	-	-	-	-	-	-	-
Valine	I	I	-	-	-	-	-	-	-	-	-	-
Hydroxybut-yrate	-	-	-	-	-	-	-	-	-	-	-	-
Pyruvate	O	O	O	O	O	O	O	O	O	O	O	O
Lactate	O	O	O	O	O	O	O	O	O	O	O	O
Albumin	O	O	O	O	O	O	O	O	O	O	O	O

Table 6

Disease	Enzyme Deficiency	Reaction Constrained
McArdle's disease	phosphorylase	GBE1
Tarui's disease	phosphofructokianse	PFKL
Phosphoglycerate kinase deficiency	phosphoglycerate kinase	PGK1R
Phosphoglycerate mutase deficiency	phosphoglycerate mutase	PGAM3R
Lactate dehydrogenase deficiency	Lactate dehyrogenase	LDHAR

The skeletal muscle model was tested for utilization of various carbon sources available during various stages of exercise and food starvation (Table 5). The by-product secretion of the network in an aerobic to anaerobic shift was qualitatively compared to physiological outcome of exercise and found to exhibit the same general features such as secretion of fermentative by-products and lowered energy yield.

The network behavior was also examined for five disease cases (Table 6). The test cases were chosen based on their physiological relevance to the model's predictive capabilities. In brief, McArdle's disease is marked by the impairment of glycogen breakdown. Tarui's disease is characterized by a deficiency in phosphofructokinase. The remaining diseases examined are marked by a deficiency of metabolic enzymes phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase. In each case, the changes in flux and by-product secretion of metabolites were examined for an aerobic to anaerobic metabolic shift with glycogen and

phosphocreatine as the sole carbon sources to the network and pyruvate, lactate, and albumin as the only metabolic by-products allowed to leave the system. To simulate the disease cases, the corresponding deficient enzyme was constrained to zero. In all cases, a severe reduction in energy production was demonstrated during exercise, representing the state of the disease as seen in clinical cases.

Throughout this application various publications have been referenced. The disclosures of these publications in their entireties are hereby incorporated by reference in this application in order to more fully describe the state of the art to which this invention pertains.

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.

Table 1

Locus ID	Gene Ab.	Reaction Stoichiometry	E.C.
1. Carbohydrate Metabolism			
1.1 Glycolysis / Gluconeogenesis [PATH:hsa00010]			
3098	HK1	GLC + ATP -> G6P + ADP	2.7.1.1
3099	HK2	GLC + ATP -> G6P + ADP	2.7.1.1
3101	HK3	GLC + ATP -> G6P + ADP	2.7.1.1
2645	GCK, HK4, MODY2, NIDDM	GLC + ATP -> G6P + ADP	2.7.1.2
2538	G6PC, G6PT	G6P + H2O -> GLC + PI	3.1.3.9
2821	GPI	G6P <-> F6P	5.3.1.9
5211	PFKL	F6P + ATP -> FDP + ADP	2.7.1.11
5213	PFKM	F6P + ATP -> FDP + ADP	2.7.1.11
5214	PFKP, PFK-C	F6P + ATP -> FDP + ADP	2.7.1.11
5215	PFKX	F6P + ATP -> FDP + ADP	2.7.1.11
2203	FBP1, FBP	FDP + H2O -> F6P + PI	3.1.3.11
8789	FBP2	FDP + H2O -> F6P + PI	3.1.3.11
226	ALDOA	FDP <-> T3P2 + T3P1	4.1.2.13
229	ALDOB	FDP <-> T3P2 + T3P1	4.1.2.13
230	ALDOC	FDP <-> T3P2 + T3P1	4.1.2.13
7167	TPI1	T3P2 <-> T3P1	5.3.1.1
2597	GAPD, GAPDH	T3P1 + PI + NAD <-> NADH + 13PDG	1.2.1.12
26330	GAPDS, GAPDH-2	T3P1 + PI + NAD <-> NADH + 13PDG	1.2.1.12
5230	PGK1, PGKA	13PDG + ADP <-> 3PG + ATP	2.7.2.3
5233	PGK2	13PDG + ADP <-> 3PG + ATP	2.7.2.3
5223	PGAM1, PGAMA	13PDG -> 23PDG	5.4.2.4
		23PDG + H2O -> 3PG + PI	3.1.3.13
		3PG <-> 2PG	5.4.2.1
5224	PGAM2, PGAMM	13PDG <-> 23PDG	5.4.2.4
		23PDG + H2O -> 3PG + PI	3.1.3.13
		3PG <-> 2PG	5.4.2.1
669	BPGM	13PDG <-> 23PDG	5.4.2.4
		23PDG + H2O <-> 3PG + PI	3.1.3.13
		3PG <-> 2PG	5.4.2.1
2023	ENO1, PPH, ENO1L1	2PG <-> PEP + H2O	4.2.1.11
2026	ENO2	2PG <-> PEP + H2O	4.2.1.11
2027	ENO3	2PG <-> PEP + H2O	4.2.1.11
26237	ENO1B	2PG <-> PEP + H2O	4.2.1.11
5313	PKLR, PK1	PEP + ADP -> PYR + ATP	2.7.1.40
5315	PKM2, PK3, THBP1, OIP3	PEP + ADP -> PYR + ATP	2.7.1.40
5160	PDHA1, PHE1A, PDHA	PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	1.2.4.1
5161	PDHA2, PDHAL	PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	1.2.4.1
5162	PDHB	PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	1.2.4.1
1737	DLAT, DLTA, PDC-E2	PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	2.3.1.12
8050	PDX1, E3BP	PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	2.3.1.12
3939	LDHA, LDH1	NAD + LAC <-> PYR + NADH	1.1.1.27
3945	LDHB	NAD + LAC <-> PYR + NADH	1.1.1.27
3948	LDHC, LDH3	NAD + LAC <-> PYR + NADH	1.1.1.27
5236	PGM1	G1P <-> G6P	5.4.2.2
5237	PGM2	G1P <-> G6P	5.4.2.2
5238	PGM3	G1P <-> G6P	5.4.2.2
1738	DLD, LAD, PHE3, DLDH, E3	DLIPOm + FADm <-> LIPOm + FADH2m	1.8.1.4
124	ADH1	ETH + NAD <-> ACAL + NADH	1.1.1.1
125	ADH2	ETH + NAD <-> ACAL + NADH	1.1.1.1
126	ADH3	ETH + NAD <-> ACAL + NADH	1.1.1.1
127	ADH4	ETH + NAD <-> ACAL + NADH	1.1.1.1
128	ADH5	FALD + RGT + NAD <-> FGT + NADH	1.2.1.1
		ETH + NAD <-> ACAL + NADH	1.1.1.1
130	ADH6	ETH + NAD <-> ACAL + NADH	1.1.1.1
131	ADH7	ETH + NAD <-> ACAL + NADH	1.1.1.1
10327	AKR1A1, ALR, ALDR1		1.1.1.2
97	ACYP1		3.6.1.7
98	ACYP2		3.6.1.7
1.2 Citrate cycle (TCA cycle) PATH:hsa00020			
1431	CS	ACCOAm + OAm + H2Om -> COAm + CITm	4.1.3.7
48	ACO1, IREB1, IRP1	CIT <-> ICIT	4.2.1.3
50	ACO2	CITm <-> ICITm	4.2.1.3
3417	IDH1	ICIT + NADP -> NADPH + CO2 + AKG	1.1.1.42

3418 IDH2	ICITm + NADPm -> NADPHm + CO2m + AKGm	1.1.1.42
3419 IDH3A	ICITm + NADm -> CO2m + NADHm + AKGm	1.1.1.41
3420 IDH3B	ICITm + NADm -> CO2m + NADHm + AKGm	1.1.1.41
3421 IDH3G	ICITm + NADm -> CO2m + NADHm + AKGm	1.1.1.41
4967 OGDH	AKGm + NADm + COAm -> CO2m + NADHm + SUCCOAm	1.2.4.2
1743 DLST, DLTS	AKGm + NADm + COAm -> CO2m + NADHm + SUCCOAm	2.3.1.61
8802 SUCLG1, SUCLA1	GTPm + SUCCm + COAm <-> GDPm + PIm + SUCCOAm	6.2.1.4
8803 SUCLA2	ATPm + SUCCm + COAm <-> ADPm + PIm + SUCCOAm	6.2.1.4
2271 FH	FUMm + H2Om <-> MALm	4.2.1.2
4190 MDH1	MAL + NAD <-> NADH + OA	1.1.1.37
4191 MDH2	MALm + NADm <-> NADHm + OAm	1.1.1.37
5091 PC, PCB	PYRm + ATPm + CO2m -> ADPm + OAm + PIm	6.4.1.1
47 ACLY, ATPCL, CLATP	ATP + CIT + COA + H2O -> ADP + PI + ACCOA + OA	4.1.3.8
3657		
5105 PCK1	OA + GTP -> PEP + GDP + CO2	4.1.1.32
5106 PCK2, PEPCK	OAm + GTPm -> PEPm + GDPm + CO2m	4.1.1.32
1.3 Pentose phosphate cycle PATH:hsa00030		
2539 G6PD, G6PD1	G6P + NADP <-> D6PGL + NADPH	1.1.1.49
9563 H6PD		1.1.1.47
	D6PGL + H2O -> D6PGC	3.1.1.31
25796 PGLS, 6PGL	D6PGL + H2O -> D6PGC	3.1.1.31
5226 PGD	D6PGC + NADP -> NADPH + CO2 + RL5P	1.1.1.44
6120 RPE	RL5P <-> X5P	5.1.3.1
7086 TKT	R5P + X5P <-> T3P1 + S7P	2.2.1.1
	X5P + E4P <-> F6P + T3P1	
8277 TKTL1, TKR, TKT2	R5P + X5P <-> T3P1 + S7P	2.2.1.1
	X5P + E4P <-> F6P + T3P1	
6888 TALDO1	T3P1 + S7P <-> E4P + F6P	2.2.1.2
5631 PRPS1, PRS I, PRS, I	R5P + ATP <-> PRPP + AMP	2.7.6.1
5634 PRPS2, PRS II, PRS, II	R5P + ATP <-> PRPP + AMP	2.7.6.1
2663 GDH		1.1.1.47
1.4 Pentose and glucuronate interconversions PATH:hsa00040		
231 AKR1B1, AR, ALDR1, ADR		1.1.1.21
7359 UGP1	G1P + UTP -> UDPG + PPI	2.7.7.9
7360 UGP2, UGPP2	G1P + UTP -> UDPG + PPI	2.7.7.9
7358 UGDH, UDPGDH		1.1.1.22
10720 UGT2B11		2.4.1.17
54658 UGT1A1, UGT1A, GNT1, UGT1		2.4.1.17
7361 UGT1A, UGT1, UGT1A		2.4.1.17
7362 UGT2B, UGT2, UGT2B		2.4.1.17
7363 UGT2B4, UGT2B11		2.4.1.17
7364 UGT2B7, UGT2B9		2.4.1.17
7365 UGT2B10		2.4.1.17
7366 UGT2B15, UGT2B8		2.4.1.17
7367 UGT2B17		2.4.1.17
13 AADAC, DAC		3.1.1.-
3991 LIPE, LHS, HSL		3.1.1.-
1.5 Fructose and mannose metabolism PATH:hsa00051		
4351 MPI, PMI1	MAN6P <-> F6P	5.3.1.8
5372 PMM1	MAN6P <-> MAN1P	5.4.2.8
5373 PMM2, CDG1, CDGS	MAN6P <-> MAN1P	5.4.2.8
2762 GMDS		4.2.1.47
8790 FPGT, GFPP		2.7.7.30
5207 PFKFB1, PFRX	ATP + F6P -> ADP + F26P	2.7.1.105
	F26P -> F6P + PI	3.1.3.46
5208 PFKFB2	ATP + F6P -> ADP + F26P	2.7.1.105
	F26P -> F6P + PI	3.1.3.46
5209 PFKFB3	ATP + F6P -> ADP + F26P	2.7.1.105
	F26P -> F6P + PI	3.1.3.46
5210 PFKFB4	ATP + F6P -> ADP + F26P	2.7.1.105
	F26P -> F6P + PI	3.1.3.46
3795 KHK		2.7.1.3
6652 SORD	DSOT + NAD -> FRU + NADH	1.1.1.14
2526 FUT4, FCT3A, FUC-TIV		2.4.1.-
2529 FUT7		2.4.1.-
3036 HAS1, HAS		2.4.1.-
3037 HAS2		2.4.1.-

8473 OGT, O-GLCNAC		2.4.1.-
51144 LOC51144		1.1.1.-
1.6 Galactose metabolism PATH:hsa00052		
2584 GALK1, GALK	GLAC + ATP -> GAL1P + ADP	2.7.1.6
2585 GALK2, GK2	GLAC + ATP -> GAL1P + ADP	2.7.1.6
2592 GALT	UTP + GAL1P <-> PPI + UDPGAL	2.7.7.10
2582 GALE	UDPGAL <-> UDPG	5.1.3.2
2720 GLB1		3.2.1.23
3938 LCT, LAC		3.2.1.62
		3.2.1.108
2683 B4GALT1, GGTB2, BETA4GAL-T1, GT1, GTB		2.4.1.90
		2.4.1.38
		2.4.1.22
3906 LALBA		2.4.1.22
2717 GLA, GALA	MELI -> GLC + GLAC	3.2.1.22
2548 GAA	MLT -> 2 GLC	3.2.1.20
	6DGLC -> GLAC + GLC	
2594 GANAB	MLT -> 2 GLC	3.2.1.20
	6DGLC -> GLAC + GLC	
2595 GANC	MLT -> 2 GLC	3.2.1.20
	6DGLC -> GLAC + GLC	
8972 MGAM, MG, MGA	MLT -> 2 GLC	3.2.1.20
	6DGLC -> GLAC + GLC	
		3.2.1.3
1.7 Ascorbate and aldarate metabolism PATH:hsa00053		
216 ALDH1, PUMB1	ACAL + NAD -> NADH + AC	1.2.1.3
217 ALDH2	ACALm + NADm -> NADHm + ACm	1.2.1.3
219 ALDH5, ALDHX		1.2.1.3
223 ALDH9, E3		1.2.1.3
		1.2.1.19
224 ALDH10, FALDH, SLS		1.2.1.3
8854 RALDH2		1.2.1.3
1591 CYP24		1.14.-.-
1592 CYP26A1, P450RAI		1.14.-.-
1593 CYP27A1, CTX, CYP27		1.14.-.-
1594 CYP27B1, PDDR, VDD1, VDR, CYP1, VDDR, I, P450C1		1.14.-.-
1.8 Pyruvate metabolism PATH:hsa00620		
54988 FLJ20581	ATP + AC + COA -> AMP + PPI + ACCOA	6.2.1.1
31 ACACA, ACAC, ACC	ACCOA + ATP + CO2 <-> MALCOA + ADP + PI + H	6.4.1.2
		6.3.4.14
32 ACACB, ACCB, HACC275, ACC2	ACCOA + ATP + CO2 <-> MALCOA + ADP + PI + H	6.4.1.2
		6.3.4.14
2739 GLO1, GLYI	RGT + MTHGXL <-> LGT	4.4.1.5
3029 HAGH, GLO2	LGT -> RGT + LAC	3.1.2.6
2223 FDH	FALD + RGT + NAD <-> FGT + NADH	1.2.1.1
9380 GRHPR, GLXR		1.1.1.79
4200 ME2	MALm + NADm -> CO2m + NADHm + PYRm	1.1.1.38
10873 ME3	MALm + NADPm -> CO2m + NADPHm + PYRm	1.1.1.40
29897 HUMNDME	MAL + NADP -> CO2 + NADPH + PYR	1.1.1.40
4199 ME1	MAL + NADP -> CO2 + NADPH + PYR	1.1.1.40
38 ACAT1, ACAT, T2, THIL, MAT	2 ACCOAm <-> COAm + AACCOAm	2.3.1.9
39 ACAT2	2 ACCOAm <-> COAm + AACCOAm	2.3.1.9
1.9 Glyoxylate and dicarboxylate metabolism PATH:hsa00630		
5240 PGP		3.1.3.18
2758 GLYD	3HPm + NADHm -> NADm + GLYAm	1.1.1.29
10797 MTHFD2, NMDMC	METHF <-> FTHF	3.5.4.9
	METTHF + NAD -> METHF + NADH	1.5.1.15
4522 MTHFD1	METTHF + NADP <-> METHF + NADPH	1.5.1.15
	METHF <-> FTHF	3.5.4.9
	THF + FOR + ATP -> ADP + PI + FTHF	6.3.4.3
1.10 Propanoate metabolism PATH:hsa00640		
34 ACADM, MCAD	MBCOAm + FADm -> MCCOAm + FADH2m	1.3.99.3
	IBCOAm + FADm -> MACOAm + FADH2m	
	IVCOAm + FADm -> MCRCOAm + FADH2m	
36 ACADSB	MBCOAm + FADm -> MCCOAm + FADH2m	1.3.99.3

	IBCOAm + FADm -> MACOAm + FADH2m	
	IVCOAm + FADm -> MCRCOAm + FADH2m	
1892 ECHS1, SCEH	MACOAm + H2Om -> HIBCOAm	4.2.1.17
	MCCOAm + H2Om -> MHVCOAm	
1962 EHHADH	MHVCOAm + NADm -> MAACOAm + NADHm	1.1.1.35
	HIBm + NADm -> MMAm + NADHm	
	MACOAm + H2Om -> HIBCOAm	4.2.1.17
	MCCOAm + H2Om -> MHVCOAm	
3030 HADHA, MTPA, GBP	MHVCOAm + NADm -> MAACOAm + NADHm	1.1.1.35
	HIBm + NADm -> MMAm + NADHm	
	MACOAm + H2Om -> HIBCOAm	4.2.1.17
	MCCOAm + H2Om -> MHVCOAm	
	C160CARm + COAm + FADm + NADm -> FADH2m + NADHm + C140COAm + ACCOAm	1.1.1.35 4.2.1.17
23417 MLYCD, MCD		4.1.1.9
18 ABAT, GABAT	GABA + AKG -> SUCCSAL + GLU	2.6.1.19
5095 PCCA	PROPCOAm + CO2m + ATPm -> ADPm + PIm + DMMCOAm	6.4.1.3
5096 PCCB	PROPCOAm + CO2m + ATPm -> ADPm + PIm + DMMCOAm	6.4.1.3
4594 MUT, MCM	LMMCOAm -> SUCCOAm	5.4.99.2
4329 MMSDH	MMAm + COAm + NADm -> NADHm + CO2m + PROPCOAm	1.2.1.27
8523 FACVL1, VLCS, VLACS		6.2.1.-
1.11 Butanoate metabolism PATH:hsa00650		
3028 HADH2, ERAB	C140COAm + 7 COAm + 7 FADm + 7 NADm -> 7 FADH2m + 7 NADHm + 7 ACCOAm	1.1.1.35
3033 HADHSC, SCHAD		1.1.1.35
35 ACADS, SCAD	MBCOAm + FADm -> MCCOAm + FADH2m	1.3.99.2
	IBCOAm + FADm -> MACOAm + FADH2m	
7915 ALDH5A1, SSADH, SSDH		1.2.1.24
2571 GAD1, GAD, GAD67, GAD25	GLU -> GABA + CO2	4.1.1.15
2572 GAD2	GLU -> GABA + CO2	4.1.1.15
2573 GAD3	GLU -> GABA + CO2	4.1.1.15
3157 HMGCS1, HMGCS	H3MCOA + COA <-> ACCOA + AACCOA	4.1.3.5
3158 HMGCS2	H3MCOA + COA <-> ACCOA + AACCOA	4.1.3.5
3155 HMGCL, HL	H3MCOAm -> ACCOAm + ACTACm	4.1.3.4
5019 OXCT		2.8.3.5
622 BDH	3HBm + NADm -> NADHm + Hm + ACTACm	1.1.1.30
1629 DBT, BCATE2	OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m	2.3.1.-
	OIVALm + COAm + NADm -> IBCOAm + NADHm + CO2m	
	OICAPm + COAm + NADHm -> IVCOAm + NADHm + CO2m	
1.13 Inositol metabolism PATH:hsa00031		
2. Energy Metabolism		
2.1 Oxidative phosphorylation PATH:hsa00190		
4535 MTND1	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4536 MTND2	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4537 MTND3	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4538 MTND4	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4539 MTND4L	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4540 MTND5	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4541 MTND6	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4694 NDUFA1, MWFE	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4695 NDUFA2, B8	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4696 NDUFA3, B9	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4697 NDUFA4, MLRQ	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4698 NDUFA5, UQOR13, B13	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4700 NDUFA6, B14	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4701 NDUFA7, B14.5a, B14.5A	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4702 NDUFA8, PGIV	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4704 NDUFA9, NDUFS2L	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4705 NDUFA10	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3

	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4706 NDUFAB1, SDAP	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4707 NDUFB1, MNLL, CI-SGDH	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4708 NDUFB2, AGGG	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4709 NDUFB3, B12	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4710 NDUFB4, B15	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4711 NDUFB5, SGDH	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4712 NDUFB6, B17	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4713 NDUFB7, B18	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4714 NDUFB8, ASHI	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4715 NDUFB9, UQOR22, B22	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4716 NDUFB10, PDSW	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4717 NDUFC1, KFYI	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4718 NDUFC2, B14.5b, B14.5B	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4724 NDUFS4, AQDQ	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4725 NDUFS5	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4726 NDUFS6	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4731 NDUFV3	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4727 NDUFS7, PSST	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4722 NDUFS3	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4720 NDUFS2	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4729 NDUFV2	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4723 NDUFV1, UQOR1	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
4719 NDUFS1, PRO1304	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
4728 NDUFS8	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.5.3
	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	1.6.99.3
6391 SDHC	SUCCm + FADm <-> FUMm + FADH2m	1.3.5.1
	FADH2m + Qm <-> FADm + QH2m	
6392 SDHD, CBT1, PGL, PGL1	SUCCm + FADm <-> FUMm + FADH2m	1.3.5.1
	FADH2m + Qm <-> FADm + QH2m	
6389 SDHA, SDH2, SDHF, FP	SUCCm + FADm <-> FUMm + FADH2m	1.3.5.1
	FADH2m + Qm <-> FADm + QH2m	
6390 SDHB, SDH1, IP, SDH	SUCCm + FADm <-> FUMm + FADH2m	1.3.5.1
	FADH2m + Qm <-> FADm + QH2m	
7386 UQCRFS1, RIS1	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
4519 MTCYB	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
1537 CYC1	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
7384 UQCRC1, D3S3191	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
7385 UQCRC2	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
7388 UQCRH	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
7381 UQCRB, QPC, UQBP, QP-C	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
27089 QP-C	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
10975 UQCR	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	1.10.2.2
1333 COX5BL4	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
4514 MTCO3	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
4512 MTCO1	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1

4513 MTCO2	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1329 COX5B	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1327 COX4	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1337 COX6A1, COX6A	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1339 COX6A2	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1340 COX6B	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1345 COX6C	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
9377 COX5A, COX, VA, COX-VA	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1346 COX7A1, COX7AM, COX7A	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1347 COX7A2, COX VIIa-L	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1348 COX7A3	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1349 COX7B	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
9167 COX7A2L, COX7RP, EB1	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1350 COX7C	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
1351 COX8, COX VIII	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	1.9.3.1
4508 MTATP6	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
4509 MTATP8	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
499 ATP5A2	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
507 ATP5BL1, ATPSBL1	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
508 ATP5BL2, ATPSBL2	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
519 ATP5H	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
537 ATP6S1, ORF, VATPS1, XAP-3	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
514 ATP5E	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
513 ATP5D	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
506 ATP5B, ATPSB	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
509 ATP5C1, ATP5C	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
498 ATP5A1, ATP5A, ATPM, OMR, HATP1	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
539 ATP5O, ATPO, OSCP	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
516 ATP5G1, ATP5G	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
517 ATP5G2	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
518 ATP5G3	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
515 ATP5F1	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
521 ATP5I	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
522 ATP5J, ATP5A, ATPM, ATP5	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
9551 ATP5J2, ATP5JL, F1FO-ATPASE	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
10476 ATP5JD	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
10632 ATP5JG	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
9296 ATP6S14	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
528 ATP6D	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
523 ATP6A1, VPP2	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
524 ATP6A2, VPP2	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
525 ATP6B1, VPP3, VATB	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
526 ATP6B2, VPP3	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
529 ATP6E	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
527 ATP6C, ATPL	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
533 ATP6F	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
10312 TCIRG1, TIRC7, OC-116, OC-116kDa, OC-116KDA, ATP6N1C	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
23545 TJ6	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
50617 ATP6N1B	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
535 ATP6N1	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
51382 VATD	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
8992 ATP6H	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
9550 ATP6J	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
51606 LOC51606	ADPm + Pim + 3 H -> ATPm + 3 Hm + H2Om	3.6.1.34
495 ATP4A, ATP6A	ATP + H + Kxt + H2O <-> ADP + PI + Hext + K	3.6.1.36
496 ATP4B, ATP6B	ATP + H + Kxt + H2O <-> ADP + PI + Hext + K	3.6.1.36
476 ATP1A1	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
477 ATP1A2	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
478 ATP1A3	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
479 ATP1AL1	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
23439 ATP1B4	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
481 ATP1B1, ATP1B	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
482 ATP1B2, AMOG	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
483 ATP1B3	ATP + 3 NA + 2 Kxt + H2O <-> ADP + 3 NAxt + 2 K + PI	3.6.1.37
27032 ATP2C1, ATP2C1A, PMR1	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38

487 ATP2A1, SERCA1, ATP2A	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
488 ATP2A2, ATP2B, SERCA2, DAR, DD	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
489 ATP2A3, SERCA3	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
490 ATP2B1, PMCA1	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
491 ATP2B2, PMCA2	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
492 ATP2B3, PMCA3	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
493 ATP2B4, ATP2B2, PMCA4	ATP + 2 CA + H2O <-> ADP + PI + 2 CAxt	3.6.1.38
538 ATP7A, MK, MNK, OHS	ATP + H2O + Cu2 -> ADP + PI + Cu2xt	3.6.3.4
540 ATP7B, WND	ATP + H2O + Cu2 -> ADP + PI + Cu2xt	3.6.3.4
5464 PP, SID6-8061	PPI -> 2 PI	3.6.1.1
2.2 Photosynthesis PATH:hsa00195		
2.3 Carbon fixation PATH:hsa00710		
2805 GOT1	OAm + GLUm <-> ASPm + AKGm	2.6.1.1
2806 GOT2	OA + GLU <-> ASP + AKG	2.6.1.1
2875 GPT	PYR + GLU <-> AKG + ALA	2.6.1.2
2.4 Reductive carboxylate cycle (CO2 fixation) PATH:hsa00720		
2.5 Methane metabolism PATH:hsa00680		
847 CAT	2 H2O2 -> O2	1.11.1.6
4025 LPO, SPO		1.11.1.7
4353 MPO		1.11.1.7
8288 EPX, EPX-PEN, EPO, EPP		1.11.1.7
9588 KIAA0106, AOP2		1.11.1.7
6470 SHMT1, CSHMT	THF + SER <-> GLY + METTHF	2.1.2.1
6472 SHMT2, GLYA, SHMT	THFm + SERm <-> GLYm + METTHFm	2.1.2.1
51004 LOC51004	2OPMPm + O2m -> 2OPMBm 2OPMMBm + O2m -> 2OMHMBm	1.14.13.-
9420 CYP7B1	2OPMPm + O2m -> 2OPMBm 2OPMMBm + O2m -> 2OMHMBm	1.14.13.-
2.6 Nitrogen metabolism PATH:hsa00910		
11238 CA5B		4.2.1.1
23632 CA14		4.2.1.1
759 CA1		4.2.1.1
760 CA2		4.2.1.1
761 CA3, CAIII		4.2.1.1
762 CA4, CAIV		4.2.1.1
763 CA5A, CA5, CAV, CAVA		4.2.1.1
765 CA6		4.2.1.1
766 CA7		4.2.1.1
767 CA8, CALS, CARP		4.2.1.1
768 CA9, MN		4.2.1.1
770 CA11, CARP2		4.2.1.1
771 CA12		4.2.1.1
1373 CPS1	GLUm + CO2m + 2 ATPm -> 2 ADPm + 2 PIm + CAPm	6.3.4.16
275 AMT	GLYm + THFm + NADm <-> METTHFm + NADHm + CO2m + NH3m	2.1.2.10
3034 HAL, HSTD, HIS	HIS -> NH3 + URO	4.3.1.3
2746 GLUD1, GLUD	AKGm + NADHm + NH3m <-> NADm + H2Om + GLUm AKGm + NADPHm + NH3m <-> NADPm + H2Om + GLUm	1.4.1.3
8307 GLUD2	AKGm + NADHm + NH3m <-> NADm + H2Om + GLUm AKGm + NADPHm + NH3m <-> NADPm + H2Om + GLUm	1.4.1.3
2752 GLUL, GLNS	GLUm + NH3m + ATPm -> GLNm + ADPm + Pim	6.3.1.2
22842 KIAA0838	GLN -> GLU + NH3	3.5.1.2
27165 GA	GLN -> GLU + NH3	3.5.1.2
2744 GLS	GLNm -> GLUm + NH3m	3.5.1.2
440 ASNS	ASPm + ATPm + GLNm -> GLUm + ASNm + AMPm + PPIm	6.3.5.4
1491 CTH	LLCT + H2O -> CYS + HSER OBUT + NH3 <-> HSER	4.4.1.1 4.4.1.1
2.7 Sulfur metabolism PATH:hsa00920		
9060 PAPSS2, ATPSK2, SK2	APS + ATP -> ADP + PAPS SLF + ATP -> PPI + APS	2.7.1.25 2.7.7.4
9061 PAPSS1, ATPSK1, SK1	APS + ATP -> ADP + PAPS SLF + ATP -> PPI + APS	2.7.1.25 2.7.7.4
10380 BPNT1	PAP -> AMP + PI	3.1.3.7
6799 SULT1A2		2.8.2.1
6817 SULT1A1, STP1		2.8.2.1
6818 SULT1A3, STM		2.8.2.1
6822 SULT2A1, STD		2.8.2.2

6783 STE, EST		2.8.2.4
6821 SUOX		1.8.3.1
3. Lipid Metabolism		
3.1 Fatty acid biosynthesis (path 1) PATH:hsa00061		
2194 FASN		2.3.1.85
3.2 Fatty acid biosynthesis (path 2) PATH:hsa00062		
10449 ACAA2, DSAEC	MAACOAm -> ACCOAm + PROPCOAm	2.3.1.16
30 ACAA1, ACAA	MAACOA -> ACCOA + PROPCOA	2.3.1.16
3032 HADHB	MAACOA -> ACCOA + PROPCOA	2.3.1.16
3.3 Fatty acid metabolism PATH:hsa00071		
51 ACOX1, ACOX		1.3.3.6
33 ACADL, LCAD		1.3.99.13
2639 GCDH		1.3.99.7
2179 FACL1, LACS	ATP + LCCA + COA <-> AMP + PPI + ACOA	6.2.1.3
2180 FACL2, FACL1, LACS2	ATP + LCCA + COA <-> AMP + PPI + ACOA	6.2.1.3
2182 FACL4, ACS4	ATP + LCCA + COA <-> AMP + PPI + ACOA	6.2.1.3
1374 CPT1A, CPT1, CPT1-L		2.3.1.21
1375 CPT1B, CPT1-M		2.3.1.21
1376 CPT2, CPT1, CPTASE		2.3.1.21
1632 DCI		5.3.3.8
11283 CYP4F8		1.14.14.1
1543 CYP1A1, CYP1		1.14.14.1
1544 CYP1A2		1.14.14.1
1545 CYP1B1, GLC3A		1.14.14.1
1548 CYP2A6, CYP2A3		1.14.14.1
1549 CYP2A7		1.14.14.1
1551 CYP3A7		1.14.14.1
1553 CYP2A13		1.14.14.1
1554 CYP2B		1.14.14.1
1555 CYP2B6		1.14.14.1
1557 CYP2C19, CYP2C, P450IIC19		1.14.14.1
1558 CYP2C8		1.14.14.1
1559 CYP2C9, P450IIC9, CYP2C10		1.14.14.1
1562 CYP2C18, P450IIC17, CYP2C17		1.14.14.1
1565 CYP2D6		1.14.14.1
1571 CYP2E, CYP2E1, P450C2E		1.14.14.1
1572 CYP2F1, CYP2F		1.14.14.1
1573 CYP2J2		1.14.14.1
1575 CYP3A3		1.14.14.1
1576 CYP3A4		1.14.14.1
1577 CYP3A5, PCN3		1.14.14.1
1580 CYP4B1		1.14.14.1
1588 CYP19, ARO		1.14.14.1
1595 CYP51		1.14.14.1
194 AHHR, AHH		1.14.14.1
3.4 Synthesis and degradation of ketone bodies PATH:hsa00072		
3.5 Sterol biosynthesis PATH:hsa00100		
3156 HMGCR	MVL + COA + 2 NADP <-> H3MCOA + 2 NADPH	1.1.1.34
4598 MVK, MVLK	ATP + MVL -> ADP + PMVL	2.7.1.36
	CTP + MVL -> CDP + PMVL	
	GTP + MVL -> GDP + PMVL	
	UTP + MVL -> UDP + PMVL	
10654 PMVK, PMKASE, PMK, HUMPMKI	ATP + PMVL -> ADP + PPMVL	2.7.4.2
4597 MVD, MPD	ATP + PPMVL -> ADP + PI + IPPP + CO2	4.1.1.33
3422 IDI1	IPPP <-> DMPP	5.3.3.2
2224 FDPS	GPP + IPPP -> FPP + PPI	2.5.1.10
	DMPP + IPPP -> GPP + PPI	2.5.1.1
9453 GGPS1, GGPPS	DMPP + IPPP -> GPP + PPI	2.5.1.1
	GPP + IPPP -> FPP + PPI	2.5.1.10
		2.5.1.29
2222 FDFT1, DGPT	2 FPP + NADPH -> NADP + SQL	2.5.1.21
6713 SQLE	SQL + O2 + NADP -> S23E + NADPH	1.14.99.7
4047 LSS, OSC	S23E -> LNST	5.4.99.7
1728 DIA4, NMOR1, NQO1, NMORI		1.6.99.2
4835 NMOR2, NQO2		1.6.99.2
37 ACADVL, VLCAD, LCACD		1.3.99.-
3.6 Bile acid biosynthesis PATH:hsa00120		

1056	CEL, BSSL, BAL		3.1.1.3
			3.1.1.13
3988	LIPA, LAL		3.1.1.13
6646	SOAT1, ACAT, STAT, SOAT, ACAT1, ACACT		2.3.1.26
1581	CYP7A1, CYP7		1.14.13.17
6715	SRD5A1		1.3.99.5
6716	SRD5A2		1.3.99.5
6718	AKR1D1, SRD5B1, 3o5bred		1.3.99.6
570	BAAT, BAT		2.3.1.65
3.7 C21-Steroid hormone metabolism PATH:hsa00140			
1583	CYP11A, P450SCC		1.14.15.6
3283	HSD3B1, HSD3B, HSDB3	IMZYMST -> IIMZYMST + CO2	5.3.3.1
		IMZYMST -> IIZYMST + CO2	
			1.1.1.145
3284	HSD3B2	IMZYMST -> IIMZYMST + CO2	5.3.3.1
		IMZYMST -> IIZYMST + CO2	
			1.1.1.145
1589	CYP21A2, CYP21, P450C21B, CA21H, CYP21B, P450c21B		1.14.99.10
1586	CYP17, P450C17		1.14.99.9
1584	CYP11B1, P450C11, CYP11B		1.14.15.4
1585	CYP11B2, CYP11B		1.14.15.4
3290	HSD11B1, HSD11, HSD11L, HSD11B		1.1.1.146
3291	HSD11B2, HSD11K		1.1.1.146
3.8 Androgen and estrogen metabolism PATH:hsa00150			
3292	HSD17B1, EDH17B2, EDHB17, HSD17		1.1.1.62
3293	HSD17B3, EDH17B3		1.1.1.62
3294	HSD17B2, EDH17B2		1.1.1.62
3295	HSD17B4		1.1.1.62
3296	HSD17BP1, EDH17B1, EDHB17, HSD17		1.1.1.62
51478	HSD17B7, PRAP		1.1.1.62
412	STS, ARSC, ARSC1, SSDD		3.1.6.2
414	ARSD		3.1.6.1
415	ARSE, CDPX1, CDPXR, CDPX		3.1.6.1
11185	INMT		2.1.1.-
24140	JM23		2.1.1.-
29104	N6AMT1, PRED28		2.1.1.-
29960	FJH1		2.1.1.-
3276	HRMT1L2, HCP1, PRMT1		2.1.1.-
51628	LOC51628		2.1.1.-
54743	HASJ4442		2.1.1.-
27292	HSA9761		2.1.1.-
4. Nucleotide Metabolism			
4.1 Purine metabolism PATH:hsa00230			
11164	NUDT5, HYSAH1, YSA1H		3.6.1.13
5471	PPAT, GPAT	PRPP + GLN -> PPI + GLU + PRAM	2.4.2.14
2618	GART, PGFT, PRGS	PRAM + ATP + GLY <-> ADP + PI + GAR	6.3.4.13
		FGAM + ATP -> ADP + PI + AIR	6.3.3.1
		GAR + FTHF -> THF + FGAR	2.1.2.2
5198	PFAS, FGARAT, KIAA0361, PURL	FGAR + ATP + GLN -> GLU + ADP + PI + FGAM	6.3.5.3
10606	ADE2H1	CAIR + ATP + ASP <-> ADP + PI + SAICAR	6.3.2.6
		CAIR <-> AIR + CO2	4.1.1.21
5059	PAICS, AIRC, PAIS	CAIR + ATP + ASP <-> ADP + PI + SAICAR	6.3.2.6
158	ADSL	ASUC <-> FUM + AMP	4.3.2.2
471	ATIC, PURH	AICAR + FTHF <-> THF + PRFICA	2.1.2.3
		PRFICA <-> IMP	3.5.4.10
3251	HPRT1, HPRT, HGPRT	HYXAN + PRPP -> PPI + IMP	2.4.2.8
		GN + PRPP -> PPI + GMP	
3614	IMPDH1	IMP + NAD -> NADH + XMP	1.1.1.205
3615	IMPDH2	IMP + NAD -> NADH + XMP	1.1.1.205
8833	GMPS		6.3.5.2
14923			
2987	GUK1	GMP + ATP <-> GDP + ADP	2.7.4.8

	DGMP + ATP <-> DGDP + ADP GMP + DATP <-> GDP + DADP	
2988 GUK2	GMP + ATP <-> GDP + ADP DGMP + ATP <-> DGDP + ADP GMP + DATP <-> GDP + DADP	2.7.4.8
10621 RPC39		2.7.7.6
10622 RPC32		2.7.7.6
10623 RPC62		2.7.7.6
11128 RPC155		2.7.7.6
25885 DKFZP586M0122		2.7.7.6
30834 ZNRD1		2.7.7.6
51082 LOC51082		2.7.7.6
51728 LOC51728		2.7.7.6
5430 POLR2A, RPOL2, POLR2, POLRA		2.7.7.6
5431 POLR2B, POL2RB		2.7.7.6
5432 POLR2C		2.7.7.6
5433 POLR2D, HSRBP4, HSRPB4		2.7.7.6
5434 POLR2E, RPB5, XAP4		2.7.7.6
5435 POLR2F, RPB6, HRBP14.4		2.7.7.6
5436 POLR2G, RPB7		2.7.7.6
5437 POLR2H, RPB8, RPB17		2.7.7.6
5438 POLR2I		2.7.7.6
5439 POLR2J		2.7.7.6
5440 POLR2K, RPB7.0		2.7.7.6
5441 POLR2L, RPB7.6, RPB10		2.7.7.6
5442 POLRMT, APOLMT		2.7.7.6
54479 FLJ10816, Rpo1-2		2.7.7.6
55703 FLJ10388		2.7.7.6
661 BN51T		2.7.7.6
9533 RPA40, RPA39		2.7.7.6
10721 POLQ		2.7.7.7
11232 POLG2, MTPOLB, HP55, POLB		2.7.7.7
23649 POLA2		2.7.7.7
5422 POLA		2.7.7.7
5423 POLB		2.7.7.7
5424 POLD1, POLD		2.7.7.7
5425 POLD2		2.7.7.7
5426 POLE		2.7.7.7
5427 POLE2		2.7.7.7
5428 POLG		2.7.7.7
5980 REV3L, POLZ, REV3		2.7.7.7
7498 XDH		1.1.3.22 1.1.1.204
9615 GDA, KIAA1258, CYPIN, NEDASIN		3.5.4.3
2766 GMPR		1.6.6.8
51292 LOC51292		1.6.6.8
7377 UOX		1.7.3.3
6240 RRM1	ADP + RTHIO -> DADP + OTHIO GDP + RTHIO -> DGDP + OTHIO CDP + RTHIO -> DCDP + OTHIO UDP + RTHIO -> DUDP + OTHIO	1.17.4.1
6241 RRM2	ADP + RTHIO -> DADP + OTHIO GDP + RTHIO -> DGDP + OTHIO CDP + RTHIO -> DCDP + OTHIO UDP + RTHIO -> DUDP + OTHIO	1.17.4.1
4860 NP, PNP	AND + PI <-> AD + R1P GSN + PI <-> GN + R1P DA + PI <-> AD + R1P DG + PI <-> GN + R1P DIN + PI <-> HYXAN + R1P INS + PI <-> HYXAN + R1P XTSINE + PI <-> XAN + R1P	2.4.2.1
1890 ECGF1, hPD-ECGF	DU + PI <-> URA + DR1P DT + PI <-> THY + DR1P	2.4.2.4
353 APRT	AD + PRPP -> PPI + AMP	2.4.2.7
132 ADK	ADN + ATP -> AMP + ADP	2.7.1.20
1633 DCK		2.7.1.74

1716 DGUOK		2.7.1.113
203 AK1	ATP + AMP <-> 2 ADP	2.7.4.3
	GTP + AMP <-> ADP + GDP	
	ITP + AMP <-> ADP + IDP	
204 AK2	ATP + AMP <-> 2 ADP	2.7.4.3
	GTP + AMP <-> ADP + GDP	
	ITP + AMP <-> ADP + IDP	
205 AK3	ATP + AMP <-> 2 ADP	2.7.4.3
	GTP + AMP <-> ADP + GDP	
	ITP + AMP <-> ADP + IDP	
26289 AK5	ATP + AMP <-> 2 ADP	2.7.4.3
	GTP + AMP <-> ADP + GDP	
	ITP + AMP <-> ADP + IDP	
4830 NME1, NM23, NM23-H1	UDP + ATP <-> UTP + ADP	2.7.4.6
	CDP + ATP <-> CTP + ADP	
	GDP + ATP <-> GTP + ADP	
	IDP + ATP <-> ITP + IDP	
	DGDP + ATP <-> DGTP + ADP	
	DUDP + ATP <-> DUTP + ADP	
	DCDP + ATP <-> DCTP + ADP	
	DTDP + ATP <-> DTTP + ADP	
	DADP + ATP <-> DATP + ADP	
4831 NME2, NM23-H2	UDP + ATP <-> UTP + ADP	2.7.4.6
	CDP + ATP <-> CTP + ADP	
	GDP + ATP <-> GTP + ADP	
	IDP + ATP <-> ITP + IDP	
	DGDP + ATP <-> DGTP + ADP	
	DUDP + ATP <-> DUTP + ADP	
	DCDP + ATP <-> DCTP + ADP	
	DTDP + ATP <-> DTTP + ADP	
	DADP + ATP <-> DATP + ADP	
4832 NME3, DR-nm23, DR-NM23	UDP + ATP <-> UTP + ADP	2.7.4.6
	CDP + ATP <-> CTP + ADP	
	GDP + ATP <-> GTP + ADP	
	IDP + ATP <-> ITP + IDP	
	DGDP + ATP <-> DGTP + ADP	
	DUDP + ATP <-> DUTP + ADP	
	DCDP + ATP <-> DCTP + ADP	
	DTDP + ATP <-> DTTP + ADP	
	DADP + ATP <-> DATP + ADP	
4833 NME4	UDPm + ATPm <-> UTPm + ADPm	2.7.4.6
	CDPm + ATPm <-> CTPm + ADPm	
	GDPm + ATPm <-> GTPm + ADPm	
	IDPm + ATPm <-> ITPm + IDPm	
	DGDPm + ATPm <-> DGTPm + ADPm	
	DUDPm + ATPm <-> DUTPm + ADPm	
	DCDPm + ATPm <-> DCTPm + ADPm	
	DTDPm + ATPm <-> DTTPm + ADPm	
	DADPm + ATPm <-> DATPm + ADPm	
22978 NT5B, PNT5, NT5B-PENDING	AMP + H2O -> PI + ADN	3.1.3.5
	GMP -> PI + GSN	
	CMP -> CYTD + PI	
	UMP -> PI + URI	
	IMP -> PI + INS	
	DUMP -> DU + PI	
	DTMP -> DT + PI	
	DAMP -> DA + PI	
	DGMP -> DG + PI	
	DCMP -> DC + PI	
	XMP -> PI + XTSINE	
4877 NT3	AMP -> PI + ADN	3.1.3.5
	GMP -> PI + GSN	
	CMP -> CYTD + PI	
	UMP -> PI + URI	
	IMP -> PI + INS	
	DUMP -> DU + PI	
	DTMP -> DT + PI	

	DAMP -> DA + PI	
	DGMP -> DG + PI	
	DCMP -> DC + PI	
	XMP -> PI + XTSINE	
4907 NT5, CD73	AMP -> PI + ADN	3.1.3.5
	GMP -> PI + GSN	
	CMP -> CYTD + PI	
	UMP -> PI + URI	
	IMP -> PI + INS	
	DUMP -> DU + PI	
	DTMP -> DT + PI	
	DAMP -> DA + PI	
	DGMP -> DG + PI	
	DCMP -> DC + PI	
	XMP -> PI + XTSINE	
7370 UMPH2	AMP -> PI + ADN	3.1.3.5
	GMP -> PI + GSN	
	CMP -> CYTD + PI	
	UMP -> PI + URI	
	IMP -> PI + INS	
	DUMP -> DU + PI	
	DTMP -> DT + PI	
	DAMP -> DA + PI	
	DGMP -> DG + PI	
	DCMP -> DC + PI	
	XMP -> PI + XTSINE	
10846 PDE10A	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
27115 PDE7B	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5136 PDE1A	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5137 PDE1C, HCAM3	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5138 PDE2A	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5139 PDE3A, CGI-PDE	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5140 PDE3B	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	

	cCMP -> CMP	
5141 PDE4A, DPDE2	cAMP -> AMP	3.1.4.17
5142 PDE4B, DPDE4, PDEIVB	cAMP -> AMP	3.1.4.17
5143 PDE4C, DPDE1	cAMP -> AMP	3.1.4.17
5144 PDE4D, DPDE3	cAMP -> AMP	3.1.4.17
5145 PDE6A, PDEA, CGPR-A	cGMP -> GMP	3.1.4.17
5146 PDE6C, PDEA2	cGMP -> GMP	3.1.4.17
5147 PDE6D	cGMP -> GMP	3.1.4.17
5148 PDE6G, PDEG	cGMP -> GMP	3.1.4.17
5149 PDE6H	cGMP -> GMP	3.1.4.17
5152 PDE9A	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5153 PDES1B	cAMP -> AMP	3.1.4.17
	cAMP -> AMP	
	cdAMP -> dAMP	
	cIMP -> IMP	
	cGMP -> GMP	
	cCMP -> CMP	
5158 PDE6B, CSNB3, PDEB	cGMP -> GMP	3.1.4.17
8654 PDE5A	cGMP -> GMP	3.1.4.17
100 ADA	ADN -> INS + NH3	3.5.4.4
	DA -> DIN + NH3	
270 AMPD1, MADA	AMP -> IMP + NH3	3.5.4.6
271 AMPD2	AMP -> IMP + NH3	3.5.4.6
272 AMPD3	AMP -> IMP + NH3	3.5.4.6
953 ENTPD1, CD39		3.6.1.5
3704 ITPA		3.6.1.19
107 ADCY1	ATP -> cAMP + PPI	4.6.1.1
108 ADCY2, HBAC2	ATP -> cAMP + PPI	4.6.1.1
109 ADCY3, AC3, KIAA0511	ATP -> cAMP + PPI	4.6.1.1
110 ADCY4	ATP -> cAMP + PPI	4.6.1.1
111 ADCY5	ATP -> cAMP + PPI	4.6.1.1
112 ADCY6	ATP -> cAMP + PPI	4.6.1.1
113 ADCY7, KIAA0037	ATP -> cAMP + PPI	4.6.1.1
114 ADCY8, ADCY3, HBAC1	ATP -> cAMP + PPI	4.6.1.1
115 ADCY9	ATP -> cAMP + PPI	4.6.1.1
2977 GUCY1A2, GUC1A2, GC-SA2		4.6.1.2
2982 GUCY1A3, GUC1A3, GUCSA3, GC-SA3		4.6.1.2
2983 GUCY1B3, GUC1B3, GUCSB3, GC-SB3		4.6.1.2
2984 GUCY2C, GUC2C, STAR		4.6.1.2
2986 GUCY2F, GUC2F, GC-F, GUC2DL, RETGC-2		4.6.1.2
3000 GUCY2D, CORD6, GUC2D, LCA1, GUC1A4, LCA, retGC		4.6.1.2
4881 NPR1, ANPRA, GUC2A, NPRA		4.6.1.2
4882 NPR2, ANPRB, GUC2B, NPRB, NPRBi		4.6.1.2
159 ADSS	IMP + GTP + ASP -> GDP + PI + ASUC	6.3.4.4
318 NUDT2, APAH1		3.6.1.17
5167 ENPP1, M6S1, NPPS, PCA1, PC-1, PDNP1		3.6.1.9
5168 ENPP2, ATX, PD-IALPHA, PDNP2		3.6.1.9
5169 ENPP3, PD-IBETA, PDNP3		3.6.1.9
		3.1.4.1
2272 FHIT		3.6.1.29
4.2 Pyrimidine metabolism PATH:hsa00240		
790 CAD	GLN + 2 ATP + CO2 -> GLU + CAP + 2 ADP + PI	6.3.5.5
	CAP + ASP -> CAASP + PI	2.1.3.2
	CAASP <-> DOROA	3.5.2.3
1723 DHODH	DOROA + O2 <-> H2O2 + OROA	1.3.3.1
7372 UMPS, OPRT	OMP -> CO2 + UMP	4.1.1.23

	OROA + PRPP <-> PPI + OMP	2.4.2.10
51727 LOC51727	ATP + UMP <-> ADP + UDP	2.7.4.14
	CMP + ATP <-> ADP + CDP	
	DCMP + ATP <-> ADP + DCDP	
50808 AKL3L		2.7.4.10
1503 CTPS	UTP + GLN + ATP -> GLU + CTP + ADP + PI	6.3.4.2
	ATP + UTP + NH3 -> ADP + PI + CTP	
7371 UMPK, TSA903	URI + ATP -> ADP + UMP	2.7.1.48
	URI + GTP -> UMP + GDP	
	CYTD + GTP -> GDP + CMP	
7378 UP	URI + PI <-> URA + R1P	2.4.2.3
1806 DPYD, DPD		1.3.1.2
1807 DPYS, DHPase, DHPASE, DHP		3.5.2.2
51733 LOC51733		3.5.1.6
7296 TXNRD1, TXNR	OTHIO + NADPH -> NADP + RTHIO	1.6.4.5
1854 DUT	DUTP -> PPI + DUMP	3.6.1.23
7298 TYMS, TMS, TS	DUMP + METTHF -> DHF + DTMP	2.1.1.45
978 CDA, CDD	CYTD -> URI + NH3	3.5.4.5
	DC -> NH3 + DU	
1635 DCTD	DCMP <-> DUMP + NH3	3.5.4.12
7083 TK1	DU + ATP -> DUMP + ADP	2.7.1.21
	DT + ATP -> ADP + DTMP	
7084 TK2	DUm + ATPm -> DUMPm + ADPm	2.7.1.21
	DTm + ATPm -> ADPm + DTMPm	
1841 DTYMK, TYMK, CDC8	DTMP + ATP <-> ADP + DTDP	2.7.4.9
4.3 Nucleotide sugars metabolism PATH:hsa00520		
23483 TDPGD		4.2.1.46
1486 CTBS, CTB		3.2.1.-
5. Amino Acid Metabolism		
5.1 Glutamate metabolism PATH:hsa00251		
8659 ALDH4, P5CDH	P5C + NAD + H2O -> NADH + GLU	1.5.1.12
2058 EPRS, QARS, QPRS	GLU + ATP -> GTRNA + AMP + PPI	6.1.1.17
		6.1.1.15
2673 GFPT1, GFA, GFAT, GFPT	F6P + GLN -> GLU + GA6P	2.6.1.16
9945 GFPT2, GFAT2	F6P + GLN -> GLU + GA6P	2.6.1.16
5859 QARS		6.1.1.18
2729 GLCLC, GCS, GLCL	CYS + GLU + ATP -> GC + PI + ADP	6.3.2.2
2730 GLCLR	CYS + GLU + ATP -> GC + PI + ADP	6.3.2.2
2937 GSS, GSHS	GLY + GC + ATP -> RGT + PI + ADP	6.3.2.3
2936 GSR	NADPH + OGT -> NADP + RGT	1.6.4.2
5188 PET112L, PET112		6.3.5.-
5.2 Alanine and aspartate metabolism PATH:hsa00252		
4677 NARS, ASNRS	ATP + ASP + TRNA -> AMP + PPI + ASPTRNA	6.1.1.22
435 ASL	ARGSUCC -> FUM + ARG	4.3.2.1
189 AGXT, SPAT	SERm + PYRm <-> ALAm + 3HPm	2.6.1.51
	ALA + GLX <-> PYR + GLY	2.6.1.44
16 AARS		6.1.1.7
1615 DARS		6.1.1.12
445 ASS, CTLN1, ASS1	CITR + ASP + ATP <-> AMP + PPI + ARGSUCC	6.3.4.5
443 ASPA, ASP, ACY2		3.5.1.15
1384 CRAT, CAT1		2.3.1.7
	ACCOA + CAR -> COA + ACAR	
8528 DDO		1.4.3.1
5.3 Glycine, serine and threonine metabolism PATH:hsa00260		
5723 PSPH, PSP	3PSER + H2O -> PI + SER	3.1.3.3
29968 PSA	PHP + GLU <-> AKG + 3PSER	2.6.1.52
	OHB + GLU <-> PHT + AKG	
26227 PHGDH, SERA, PGDH, PGD, PGAD	3PG + NAD <-> NADH + PHP	1.1.1.95
23464 GCAT, KBL		2.3.1.29
211 ALAS1, ALAS	SUCCOA + GLY -> ALAV + COA + CO2	2.3.1.37
212 ALAS2, ANH1, ASB	SUCCOA + GLY -> ALAV + COA + CO2	2.3.1.37
4128 MAOA	AMA + H2O + FAD -> NH3 + FADH2 + MTHGXL	1.4.3.4
4129 MAOB	AMA + H2O + FAD -> NH3 + FADH2 + MTHGXL	1.4.3.4
26 ABP1, AOC1, DAO		1.4.3.6
314 AOC2, DAO2, RAO		1.4.3.6
8639 AOC3, VAP-1, VAP1, HPAO		1.4.3.6
2731 GLDC	GLY + LIPO <-> SAP + CO2	1.4.4.2

1610	DAO, DAMOX		1.4.3.3
2617	GARS		6.1.1.14
2628	GATM		2.1.4.1
2593	GAMT		2.1.1.2
23761	PISD, PSSC, DKFZP566G2246, DJ858B16	PS -> PE + CO2	4.1.1.65
635	BHMT		2.1.1.5
29958	DMGDH		1.5.99.2
875	CBS	SER + HCYS -> LLCT + H2O	4.2.1.22
6301	SARS, SERS		6.1.1.11
10993	SDS, SDH	SER -> PYR + NH3 + H2O	4.2.1.13
6897	TARS		6.1.1.3
5.4 Methionine metabolism PATH:hsa00271			
4143	MAT1A, MATA1, SAMS1, MAT, SAMS	MET + ATP + H2O -> PPI + PI + SAM	2.5.1.6
4144	MAT2A, MATA2, SAMS2, MATII	MET + ATP + H2O -> PPI + PI + SAM	2.5.1.6
1786	DNMT1, MCMT, DNMT	SAM + DNA -> SAH + DNA5MC	2.1.1.37
10768	AHCYL1, XPVKONA	SAH + H2O -> HCYS + ADN	3.3.1.1
191	AHCY, SAHH	SAH + H2O -> HCYS + ADN	3.3.1.1
4141	MARS, METRS, MTRNS		6.1.1.10
4548	MTR	HCYS + MTHF -> THF + MET	2.1.1.13
5.5 Cysteine metabolism PATH:hsa00272			
833	CARS		6.1.1.16
1036	CDO1	CYS + O2 <-> CYSS	1.13.11.20
8509	NDST2, HSST2, NST2		2.8.2.-
5.6 Valine, leucine and isoleucine degradation PATH:hsa00280			
586	BCAT1, BCT1, ECA39, MECA39	AKG + ILE -> OMVAL + GLU AKG + VAL -> OIVAL + GLU AKG + LEU -> OICAP + GLU	2.6.1.42
587	BCAT2, BCT2	OICAPm + GLUm <-> AKGm + LEUm OMVALm + GLUm <-> AKGm + ILEm	2.6.1.42
5014	OVD1A		1.2.4.4
593	BCKDHA, MSUD1	OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m OIVALm + COAm + NADm -> IBCOAm + NADHm + CO2m OICAPm + COAm + NADm -> IVCOAm + NADHm + CO2m	1.2.4.4
594	BCKDHB, E1B	OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m OIVALm + COAm + NADm -> IBCOAm + NADHm + CO2m OICAPm + COAm + NADH -> IVCOAm + NADHm + CO2m	1.2.4.4
3712	IVD	IVCOAm + FADm -> MCRCOAm + FADH2m	1.3.99.10
316	AOX1, AO		1.2.3.1
4164	MCCC1	MCRCOAm + ATPm + CO2m + H2Om -> MGCOAm + ADPm + Pim	6.4.1.4
4165	MCCC2	MCRCOAm + ATPm + CO2m + H2Om -> MGCOAm + ADPm + Pim	6.4.1.4
5.7 Valine, leucine and isoleucine biosynthesis PATH:hsa00290			
23395	KIAA0028, LARS2		6.4.1.4
3926	LARS		6.4.1.4
3376	IARS, ILRS		6.1.1.5
7406	VARS1, VARS		6.1.1.9
7407	VARS2, G7A		6.1.1.9
5.8 Lysine biosynthesis PATH:hsa00300			
3735	KARS, KIAA0070	ATP + LYS + LTRNA -> AMP + PPI + LLTRNA	6.1.1.6
5.9 Lysine degradation PATH:hsa00310			
8424	BBOX, BBH, GAMMA-BBH, G-BBH		1.14.11.1
5351	PLOD, LLH		1.14.11.4
5352	PLOD2		1.14.11.4
8985	PLOD3, LH3		1.14.11.4
10157	LKR/SDH, AASS	LYS + NADPH + AKG -> NADP + H2O + SAC SAC + H2O + NAD -> GLU + NADH + AASA	1.5.1.9
5.10 Arginine and proline metabolism PATH:hsa00330			
5009	OTC	ORNm + CAPm -> CITRm + Pim + Hm	2.1.3.3
383	ARG1	ARG -> ORN + UREA	3.5.3.1
384	ARG2	ARG -> ORN + UREA	3.5.3.1
4842	NOS1, NOS		1.14.13.39
4843	NOS2A, NOS2		1.14.13.39
4846	NOS3, ECNOS		1.14.13.39
4942	OAT	ORN + AKG <-> GLUGSAL + GLU	2.6.1.13

5831 PYCR1, P5C, PYCR	P5C + NADPH -> PRO + NADP P5C + NADH -> PRO + NAD PHC + NADPH -> HPRO + NADP PHC + NADH -> HPRO + NAD	1.5.1.2
5033 P4HA1, P4HA		1.14.11.2
5917 RARS	ATP + ARG + ATRNA -> AMP + PPI + ALTRNA	6.1.1.19
1152 CKB, CKBB	PCRE + ADP -> CRE + ATP	2.7.3.2
1156 CKBE		2.7.3.2
1158 CKM, CKMM		2.7.3.2
1159 CKMT1, CKMT, UMTCK		2.7.3.2
1160 CKMT2, SMTCK		2.7.3.2
6723 SRM, SPS1, SRML1	PTRSC + SAM -> SPRMD + 5MTA	2.5.1.16
262 AMD1, ADOMETDC	SAM <-> DSAM + CO2	4.1.1.50
263 AMDP1, AMD, AMD2	SAM <-> DSAM + CO2	4.1.1.50
1725 DHPS	SPRMD + Qm -> DAPRP + QH2m	1.5.99.6
6611 SMS	DSAM + SPRMD -> 5MTA + SPRM	2.5.1.22
4953 ODC1	ORN -> PTRSC + CO2	4.1.1.17
6303 SAT, SSAT		2.3.1.57
5.11 Histidine metabolism PATH:hsa00340		
10841 FTCD	FIGLU + THF -> NFTHF + GLU	2.1.2.5 4.3.1.4
3067 HDC		4.1.1.22
1644 DDC, AADC		4.1.1.28
3176 HNMT		2.1.1.8
218 ALDH3	ACAL + NAD -> NADH + AC	1.2.1.5
220 ALDH6	ACAL + NAD -> NADH + AC	1.2.1.5
221 ALDH7, ALDH4	ACAL + NAD -> NADH + AC	1.2.1.5
222 ALDH8	ACAL + NAD -> NADH + AC	1.2.1.5
3035 HARS	ATP + HIS + HTRNA -> AMP + PPI + HHTRNA	6.1.1.21
5.12 Tyrosine metabolism PATH:hsa00350		
6898 TAT	AKG + TYR -> HPHPYR + GLU	2.6.1.5
3242 HPD, PPD	HPHPYR + O2 -> HGTS + CO2	1.13.11.27
3081 HGD, AKU, HGO	HGTS + O2 -> MACA	1.13.11.5
2954 GSTZ1, MAAI	MACA -> FACA	5.2.1.2 2.5.1.18
2184 FAH	FACA + H2O -> FUM + ACA	3.7.1.2
7299 TYR, OCAIA		1.14.18.1
7054 TH, TYH		1.14.16.2
1621 DBH		1.14.17.1
5409 PNMT, PENT		2.1.1.28
1312 COMT		2.1.1.6
7173 TPO, TPX		1.11.1.8
5.13 Phenylalanine metabolism PATH:hsa00360		
501 ATQ1		1.2.1.-
5.14 Tryptophan metabolism PATH:hsa00380		
6999 TDO2, TPH2, TRPO, TDO	TRP + O2 -> FKYN	1.13.11.11
8564 KMO	KYN + NADPH + O2 -> HKYN + NADP + H2O	1.14.13.9
8942 KYNU	KYN -> ALA + AN HKYN + H2O -> HAN + ALA	3.7.1.3
23498 HAAO, HAO, 3-HAO	HAN + O2 -> CMUSA	1.13.11.6
7166 TPH, TPRH		1.14.16.4
438 ASMT, HIOMT, ASMTY		2.1.1.4
15 AANAT, SNAT		2.3.1.87
3620 INDO, IDO		1.13.11.42
10352 WARS2	ATPm + TRPm + TRNAm -> AMPm + PPIm + TRPTRNAm	6.1.1.2
7453 WARS, IFP53, IFI53, GAMMA-2	ATP + TRP + TRNA -> AMP + PPI + TRPTRNA	6.1.1.2
4734 NEDD4, KIAA0093		6.3.2.-
5.15 Phenylalanine, tyrosine and tryptophan biosynthesis PATH:hsa00400		
5053 PAH, PKU1	PHE + THBP + O2 -> TYR + DHBP + H2O	1.14.16.1
10667 FARS1		6.1.1.20
2193 FARSL, CML33		6.1.1.20
10056 PheHB		6.1.1.20
8565 YARS, TYRRS, YTS, YRS		6.1.1.1
5.16 Urea cycle and metabolism of amino groups PATH:hsa00220		
5832 PYCS		2.7.2.11
	GLUP + NADH -> NAD + PI + GLUGSAL GLUP + NADPH -> NADP + PI + GLUGSAL	1.2.1.41

95	ACY1		3.5.1.14

6. Metabolism of Other Amino Acids
6.1 beta-Alanine metabolism PATH:hsa00410
6.2 Taurine and hypotaurine metabolism PATH:hsa00430

2678	GGT1, GTG, D22S672, D22S732, GGT	RGT + ALA -> CGLY + ALAGLY	2.3.2.2
2679	GGT2, GGT	RGT + ALA -> CGLY + ALAGLY	2.3.2.2
2680	GGT3	RGT + ALA -> CGLY + ALAGLY	2.3.2.2
2687	GGTLA1, GGT-REL, DKFZP566O011	RGT + ALA -> CGLY + ALAGLY	2.3.2.2

6.3 Aminophosphonate metabolism PATH:hsa00440

5130	PCYT1A, CTPCT, CT, PCYT1	PCHO + CTP -> CDPCHO + PPI	2.7.7.15
9791	PTDSS1, KIAA0024, PSSA	CDPDG + SER <-> CMP + PS	2.7.8.-

6.4 Selenoamino acid metabolism PATH:hsa00450

22928	SPS2		2.7.9.3
22929	SPS, SELD		2.7.9.3

6.5 Cyanoamino acid metabolism PATH:hsa00460
6.6 D-Glutamine and D-glutamate metabolism PATH:hsa00471
6.7 D-Arginine and D-ornithine metabolism PATH:hsa00472
6.9 Glutathione metabolism PATH:hsa00480

5182	PEPB		3.4.11.4
2655	GCTG		2.3.2.4
2876	GPX1, GSHPX1	2 RGT + H2O2 <-> OGT	1.11.1.9
2877	GPX2, GSHPX-GI	2 RGT + H2O2 <-> OGT	1.11.1.9
2878	GPX3	2 RGT + H2O2 <-> OGT	1.11.1.9
2879	GPX4	2 RGT + H2O2 <-> OGT	1.11.1.9
2880	GPX5	2 RGT + H2O2 <-> OGT	1.11.1.9
2881	GPX6	2 RGT + H2O2 <-> OGT	1.11.1.9
2938	GSTA1		2.5.1.18
2939	GSTA2, GST2		2.5.1.18
2940	GSTA3		2.5.1.18
2941	GSTA4		2.5.1.18
2944	GSTM1, GST1, MU		2.5.1.18
2946	GSTM2, GST4		2.5.1.18
2947	GSTM3, GST5		2.5.1.18
2948	GSTM4		2.5.1.18
2949	GSTM5		2.5.1.18
2950	GSTP1, FAEES3, DFN7, GST3, PI		2.5.1.18
2952	GSTT1		2.5.1.18
2953	GSTT2		2.5.1.18
4257	MGST1, GST12, MGST, MGST-I		2.5.1.18
4258	MGST2, GST2, MGST-II		2.5.1.18
4259	MGST3, GST-III		2.5.1.18

7. Metabolism of Complex Carbohydrates
7.1 Starch and sucrose metabolism PATH:hsa00500

6476	SI		3.2.1.10 3.2.1.48
11181	TREH, TRE, TREA	TRE -> 2 GLC	3.2.1.28
2990	GUSB		3.2.1.31
2632	GBE1	GLYCOGEN + PI -> G1P	2.4.1.18
5834	PYGB	GLYCOGEN + PI -> G1P	2.4.1.1
5836	PYGL	GLYCOGEN + PI -> G1P	2.4.1.1
5837	PYGM	GLYCOGEN + PI -> G1P	2.4.1.1
2997	GYS1, GYS	UDPG -> UDP + GLYCOGEN	2.4.1.11
2998	GYS2	UDPG -> UDP + GLYCOGEN	2.4.1.11
276	AMY1A, AMY1		3.2.1.1
277	AMY1B, AMY1		3.2.1.1
278	AMY1C, AMY1		3.2.1.1
279	AMY2A, AMY2		3.2.1.1
280	AMY2B, AMY2		3.2.1.1
178	AGL, GDE		2.4.1.25 3.2.1.33
10000	AKT3, PKBG, RAC-GAMMA, PRKBG		2.7.1.-
1017	CDK2		2.7.1.-
1018	CDK3		2.7.1.-
1019	CDK4, PSK-J3		2.7.1.-
1020	CDK5, PSSALRE		2.7.1.-

1021	CDK6, PLSTIRE	2.7.1.-
1022	CDK7, CAK1, STK1, CDKN7	2.7.1.-
1024	CDK8, K35	2.7.1.-
1025	CDK9, PITALRE, CDC2L4	2.7.1.-
10298	PAK4	2.7.1.-
10746	MAP3K2, MEKK2	2.7.1.-
1111	CHEK1, CHK1	2.7.1.-
11200	RAD53, CHK2, CDS1, HUCDS1	2.7.1.-
1195	CLK1, CLK	2.7.1.-
1326	MAP3K8, COT, EST, ESTF, TPL-2	2.7.1.-
1432	MAPK14, CSBP2, CSPB1, PRKM14, PRKM15, CSBP1, P38, MXI2	2.7.1.-
1452	CSNK1A1	2.7.1.-
1453	CSNK1D, HCKID	2.7.1.-
1454	CSNK1E, HCKIE	2.7.1.-
1455	CSNK1G2	2.7.1.-
1456	CSNK1G3	2.7.1.-
1612	DAPK1, DAPK	2.7.1.-
1760	DMPK, DM, DMK, DM1	2.7.1.-
1859	DYRK1A, DYRK1, DYRK, MNB, MNBH	2.7.1.-
208	AKT2, RAC-BETA, PRKBB, PKBBETA	2.7.1.-
269	AMHR2, AMHR	2.7.1.-
27330	RPS6KA6, RSK4	2.7.1.-
2868	GPRK2L, GPRK4	2.7.1.-
2869	GPRK5, GRK5	2.7.1.-
2870	GPRK6, GRK6	2.7.1.-
29904	HSU93850	2.7.1.-
30811	HUNK	2.7.1.-
3611	ILK, P59	2.7.1.-
3654	IRAK1, IRAK	2.7.1.-
369	ARAF1, PKS2, RAFA1	2.7.1.-
370	ARAF2P, PKS1, ARAF2	2.7.1.-
3984	LIMK1, LIMK	2.7.1.-
3985	LIMK2	2.7.1.-
4117	MAK	2.7.1.-
4140	MARK3, KP78	2.7.1.-
4215	MAP3K3, MAPKKK3, MEKK3	2.7.1.-
4216	MAP3K4, MAPKKK4, MTK1, MEKK4, KIAA0213	2.7.1.-
4217	MAP3K5, ASK1, MAPKKK5, MEKK5	2.7.1.-
4293	MAP3K9, PRKE1, MLK1	2.7.1.-
4294	MAP3K10, MLK2, MST	2.7.1.-
4342	MOS	2.7.1.-
4751	NEK2, NLK1	2.7.1.-
4752	NEK3	2.7.1.-
5058	PAK1, PAKalpha	2.7.1.-
5062	PAK2, PAK65, PAKgamma	2.7.1.-
5063	PAK3, MRX30, PAK3beta	2.7.1.-
5127	PCTK1, PCTGAIRE	2.7.1.-
5128	PCTK2	2.7.1.-
5129	PCTK3, PCTAIRE	2.7.1.-
5292	PIM1, PIM	2.7.1.-
5347	PLK, PLK1	2.7.1.-
5562	PRKAA1	2.7.1.-
5563	PRKAA2, AMPK, PRKAA	2.7.1.-
5578	PRKCA, PKCA	2.7.1.-
5579	PRKCB1, PKCB, PRKCB, PRKCB2	2.7.1.-
5580	PRKCD	2.7.1.-
5581	PRKCE	2.7.1.-
5582	PRKCG, PKCC, PKCG	2.7.1.-
5583	PRKCH, PKC-L, PRKCL	2.7.1.-
5584	PRKCI, DXS1179E, PKCI	2.7.1.-
5585	PRKCL1, PAK1, PRK1, DBK, PKN	2.7.1.-
5586	PRKCL2, PRK2	2.7.1.-
5588	PRKCQ	2.7.1.-

5590	PRKCZ	2.7.1.-
5594	MAPK1, PRKM1, P41MAPK, P42MAPK, ERK2, ERK, MAPK2, PRKM2	2.7.1.-
5595	MAPK3, ERK1, PRKM3, P44ERK1, P44MAPK	2.7.1.-
5597	MAPK6, PRKM6, P97MAPK, ERK3	2.7.1.-
5598	MAPK7, BMK1, ERK5, PRKM7	2.7.1.-
5599	MAPK8, JNK, JNK1, SAPK1, PRKM8, JNK1A2	2.7.1.-
5601	MAPK9, JNK2, PRKM9, P54ASAPK, JUNKINASE	2.7.1.-
5602	MAPK10, JNK3, PRKM10, P493F12, P54BSAPK	2.7.1.-
5603	MAPK13, SAPK4, PRKM13, P38DELTA	2.7.1.-
5604	MAP2K1, MAPKK1, MEK1, MKK1, PRKMK1	2.7.1.-
5605	MAP2K2, MEK2, PRKMK2	2.7.1.-
5606	MAP2K3, MEK3, MKK3, PRKMK3	2.7.1.-
5607	MAP2K5, MEK5, PRKMK5	2.7.1.-
5608	MAP2K6, MEK6, MKK6, SAPKK3, PRKMK6	2.7.1.-
5609	MAP2K7, MAPKK7, MKK7, PRKMK7, JNKK2	2.7.1.-
5610	PRKR, EIF2AK1, PKR	2.7.1.-
5613	PRKX, PKX1	2.7.1.-
5894	RAF1	2.7.1.-
613	BCR, CML, PHL, BCR1, D22S11, D22S662	2.7.1.-
6195	RPS6KA1, HU-1, RSK, RSK1, MAPKAPK1A	2.7.1.-
6196	RPS6KA2, HU-2, MAPKAPK1C, RSK, RSK3	2.7.1.-
6197	RPS6KA3, RSK2, HU-2, HU-3, RSK, MAPKAPK1B, ISPK-1	2.7.1.-
6198	RPS6KB1, STK14A	2.7.1.-
6199	RPS6KB2, P70-BETA, P70S6KB	2.7.1.-
6300	MAPK12, ERK6, PRKM12, SAPK3, P38GAMMA, SAPK-3	2.7.1.-
6416	MAP2K4, JNKK1, MEK4, PRKMK4, SERK1, MKK4	2.7.1.-
6446	SGK	2.7.1.-
658	BMPR1B, ALK-6, ALK6	2.7.1.-
659	BMPR2, BMPR-II, BMPR3, BRK-3	2.7.1.-
673	BRAF	2.7.1.-
6792	STK9	2.7.1.-
6794	STK11, LKB1, PJS	2.7.1.-
6885	MAP3K7, TAK1	2.7.1.-
699	BUB1	2.7.1.-
701	BUB1B, BUBR1, MAD3L	2.7.1.-
7016	TESK1	2.7.1.-
7272	TTK, MPS1L1	2.7.1.-
7867	MAPKAPK3, 3PK, MAPKAP3	2.7.1.-
8408	ULK1	2.7.1.-
8558	CDK10, PISSLRE	2.7.1.-
8621	CDC2L5, CDC2L, CHED	2.7.1.-
8737	RIPK1, RIP	2.7.1.-
8814	CDKL1, KKIALRE	2.7.1.-
8899	PRP4, PR4H	2.7.1.-
9064	MAP3K6, MAPKKK6	2.7.1.-
9149	DYRK1B	2.7.1.-
92	ACVR2, ACTRII	2.7.1.-
9201	DCAMKL1, KIAA0369	2.7.1.-
93	ACVR2B	2.7.1.-
983	CDC2	2.7.1.-
984	CDC2L1	2.7.1.-

5205	FIC1, BRIC, PFIC1, PFIC, ATP8B1	DHPP -> DHP + PI GTP -> GSN + 3 PI DGTP -> DG + 3 PI	3.6.1.-
7.2 Glycoprotein biosynthesis PATH:hsa00510			
1798	DPAGT1, DPAGT, UGAT, UAGT, D11S366, DGPT, DPAGT2, GPT		2.7.8.15
29880	ALG5		2.4.1.117
8813	DPM1	GDPMAN + DOLP -> GDP + DOLMANP	2.4.1.83
1650	DDOST, OST, OST48, KIAA0115		2.4.1.119
6184	RPN1		2.4.1.119
6185	RPN2		2.4.1.119
10130	P5		5.3.4.1
10954	PDIR		5.3.4.1
11008	PDI		5.3.4.1
2923	GRP58, ERp57, ERp60, ERp61, GRP57, P58, PI-PLC, ERP57, ERP60, ERP61		5.3.4.1
5034	P4HB, PROHB, PO4DB, ERBA2L		5.3.4.1
7841	GCS1		3.2.1.106
4121	MAN1A1, MAN9, HUMM9		3.2.1.113
4245	MGAT1, GLYT1, GLCNAC-TI, GNT-I, MGAT		2.4.1.101
4122	MAN2A2, MANA2X		3.2.1.114
4124	MAN2A1, MANA2		3.2.1.114
4247	MGAT2, CDGS2, GNT-II, GLCNACTII, GNT2		2.4.1.143
4248	MGAT3, GNT-III		2.4.1.144
6487	SIAT6, ST3GALII		2.4.99.6
6480	SIAT1		2.4.99.1
2339	FNTA, FPTA, PGGT1A		2.5.1.-
2342	FNTB, FPTB		2.5.1.-
5229	PGGT1B, BGGI, GGTI		2.5.1.-
5875	RABGGTA		2.5.1.-
5876	RABGGTB		2.5.1.-
1352	COX10		2.5.1.-
7.3 Glycoprotein degradation PATH:hsa00511			
4758	NEU1, NEU		3.2.1.18
3073	HEXA, TSD		3.2.1.52
3074	HEXB		3.2.1.52
4123	MAN2C1, MANA, MANA1, MAN6A8		3.2.1.24
4125	MAN2B1, MANB, LAMAN		3.2.1.24
4126	MANBA, MANB1		3.2.1.25
2517	FUCA1		3.2.1.51
2519	FUCA2		3.2.1.51
175	AGA, AGU		3.5.1.26
7.4 Aminosugars metabolism PATH:hsa00530			
6675	UAP1, SPAG2, AGX1	UTP + NAGA1P <-> UDPNAG + PPI	2.7.7.23
10020	GNE, GLCNE		5.1.3.14
22951	CMAS		2.7.7.43
1727	DIA1		1.6.2.2
4669	NAGLU, NAG		3.2.1.50
7.5 Lipopolysaccharide biosynthesis PATH:hsa00540			
6485	SIAT5, SAT3, STZ		2.4.99.-
7903	SIAT8D, PST, PST1, ST8SIA-IV		2.4.99.-
8128	SIAT8B, STX, ST8SIA-II		2.4.99.-
7.7 Glycosaminoglycan degradation PATH:hsa00531			
3423	IDS, MPS2, SIDS		3.1.6.13
3425	IDUA, IDA		3.2.1.76
411	ARSB		3.1.6.12
2799	GNS, G6S		3.1.6.14
2588	GALNS, MPS4A, GALNAC6S, GAS		3.1.6.4
8. Metabolism of Complex Lipids			
8.1 Glycerolipid metabolism PATH:hsa00561			
10554	AGPAT1, LPAAT-ALPHA, G15	AGL3P + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> PA + ACP	2.3.1.51

10555 AGPAT2, LPAAT-BETA	AGL3P + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> PA + ACP	2.3.1.51
1606 DGKA, DAGK, DAGK1		2.7.1.107
1608 DGKG, DAGK3		2.7.1.107
1609 DGKQ, DAGK4		2.7.1.107
8525 DGKZ, DAGK5, HDGKZETA		2.7.1.107
8526 DGKE, DAGK6, DGK		2.7.1.107
8527 DGKD, DGKDELTA, KIAA0145		2.7.1.107
1120 CHKL	ATP + CHO -> ADP + PCHO	2.7.1.32
EKI1	ATP + ETHM -> ADP + PETHM	2.7.1.82
1119 CHK, CKI	ATP + CHO -> ADP + PCHO	2.7.1.32
43 ACHE, YT		3.1.1.7
1103 CHAT		2.3.1.6
5337 PLD1		3.1.4.4
26279 PLA2G2D, SPLA2S		3.1.1.4
30814 PLA2G2E		3.1.1.4
5319 PLA2G1B, PLA2, PLA2A, PPLA2		3.1.1.4
5320 PLA2G2A, MOM1, PLA2B, PLA2L		3.1.1.4
5322 PLA2G5		3.1.1.4
8398 PLA2G6, IPLA2		3.1.1.4
8399 PLA2G10, SPLA2		3.1.1.4
1040 CDS1	PA + CTP <-> CDPDG + PPI	2.7.7.41
10423 PIS	CDPDG + MYOI -> CMP + PINS	2.7.8.11
2710 GK	GL + ATP -> GL3P + ADP	2.7.1.30
2820 GPD2	GL3Pm + FADm -> T3P2m + FADH2m	1.1.99.5
2819 GPD1	T3P2 + NADH <-> GL3P + NAD	1.1.1.8
248 ALPI	AHTD -> DHP + 3 PI	3.1.3.1
249 ALPL, HOPS, TNSALP	AHTD -> DHP + 3 PI	3.1.3.1
250 ALPP	AHTD -> DHP + 3 PI	3.1.3.1
251 ALPPL2	AHTD -> DHP + 3 PI	3.1.3.1
439 ASNA1, ARSA-I		3.6.1.16
8694 DGAT, ARGP1	DAGLY + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> TAGLY + ACP	2.3.1.20
3989 LIPB		3.1.1.3
3990 LIPC, HL		3.1.1.3
5406 PNLIP		3.1.1.3
5407 PNLIPRP1, PLRP1		3.1.1.3
5408 PNLIPRP2, PLRP2		3.1.1.3
8513 LIPF, HGL, HLAL		3.1.1.3
4023 LPL, LIPD		3.1.1.34
8443 GNPAT, DHAPAT, DAP-AT		2.3.1.42
8540 AGPS, ADAP-S, ADAS, ADHAPS, ADPS, ALDHPSY		2.5.1.26
4186 MDCR, MDS, LIS1		3.1.1.47
5048 PAFAH1B1, LIS1, MDCR, PAFAH		3.1.1.47
5049 PAFAH1B2		3.1.1.47
5050 PAFAH1B3		3.1.1.47
5051 PAFAH2, HSD-PLA2		3.1.1.47
7941 PLA2G7, PAFAH, LDL-PLA2		3.1.1.47
8.2 Inositol phosphate metabolism PATH:hsa00562		
5290 PIK3CA	ATP + PINS -> ADP + PINSP	2.7.1.137
5291 PIK3CB, PIK3C1	ATP + PINS -> ADP + PINSP	2.7.1.137
5293 PIK3CD	ATP + PINS -> ADP + PINSP	2.7.1.137
5294 PIK3CG	ATP + PINS -> ADP + PINSP	2.7.1.137
5297 PIK4CA, PI4K-ALPHA	ATP + PINS -> ADP + PINS4P	2.7.1.67
5305 PIP5K2A	PINS4P + ATP -> D45PI + ADP	2.7.1.68
5330 PLCB2	D45PI -> TPI + DAGLY	3.1.4.11
5331 PLCB3	D45PI -> TPI + DAGLY	3.1.4.11
5333 PLCD1	D45PI -> TPI + DAGLY	3.1.4.11
5335 PLCG1, PLC1	D45PI -> TPI + DAGLY	3.1.4.11
5336 PLCG2	D45PI -> TPI + DAGLY	3.1.4.11
3612 IMPA1, IMPA	MI1P -> MYOI + PI	3.1.3.25
3613 IMPA2	MI1P -> MYOI + PI	3.1.3.25
3628 INPP1		3.1.3.57

3632	INPP5A		
3633	INPP5B		3.1.3.56
3636	INPPL1, SHIP2		3.1.3.56
4952	OCRL, LOCR, OCRL1, INPP5F		3.1.3.56
8867	SYNJ1, INPP5G		3.1.3.56
3706	ITPKA		2.7.1.127
51477	ISYNA1	G6P -> MI1P	5.5.1.4
3631	INPP4A, INPP4		3.1.3.66
8821	INPP4B		3.1.3.66
8.3 Sphingophospholipid biosynthesis PATH:hsa00570			
6609	SMPD1, NPD		3.1.4.12
8.4 Phospholipid degradation PATH:hsa00580			
1178	CLC		3.1.1.5
5321	PLA2G4A, CPLA2-ALPHA, PLA2G4		3.1.1.5
8.5 Sphingoglycolipid metabolism PATH:hsa00600			
10558	SPTLC1, LCB1, SPTI	PALCOA + SER -> COA + DHSPH + CO2	2.3.1.50
9517	SPTLC2, KIAA0526, LCB2	PALCOA + SER -> COA + DHSPH + CO2	2.3.1.50
427	ASAH, AC, PHP32		3.5.1.23
7357	UGCG, GCS		2.4.1.80
2629	GBA, GLUC		3.2.1.45
2583	GALGT, GALNACT		2.4.1.92
6489	SIAT8A, SIAT8, ST8SIA-I		2.4.99.8
6481	SIAT2		2.4.99.2
4668	NAGA, D22S674, GALB		3.2.1.49
9514	CST		2.8.2.11
410	ARSA, MLD		3.1.6.8
8.6 Blood group glycolipid biosynthesis - lact series PATH:hsa00601			
28	ABO		2.4.1.40
			2.4.1.37
2525	FUT3, LE		2.4.1.65
2527	FUT5, FUC-TV		2.4.1.65
2528	FUT6		2.4.1.65
2523	FUT1, H, HH		2.4.1.69
2524	FUT2, SE		2.4.1.69
8.7 Blood group glycolipid biosynthesis - neolact series PATH:hsa00602			
2651	GCNT2, IGNT, NACGT1, NAGCT1		2.4.1.150
8.8 Prostaglandin and leukotriene metabolism PATH:hsa00590			
239	ALOX12, LOG12		1.13.11.31
246	ALOX15		1.13.11.33
240	ALOX5		1.13.11.34
4056	LTC4S		2.5.1.37
4048	LTA4H		3.3.2.6
4051	CYP4F3, CYP4F, LTB4H		1.14.13.30
8529	CYP4F2		1.14.13.30
5742	PTGS1, PGHS-1		1.14.99.1
5743	PTGS2, COX-2, COX2		1.14.99.1
27306	PGDS		5.3.99.2
5730	PTGDS		5.3.99.2
5740	PTGIS, CYP8, PGIS		5.3.99.4
6916	TBXAS1, CYP5		5.3.99.5
873	CBR1, CBR		1.1.1.184
			1.1.1.189
			1.1.1.197
874	CBR3		1.1.1.184
9. Metabolism of Cofactors and Vitamins			
9.2 Riboflavin metabolism PATH:hsa00740			
52	ACP1		3.1.3.48
		FMN -> RIBOFLAV + PI	3.1.3.2
53	ACP2	FMN -> RIBOFLAV + PI	3.1.3.2
54	ACP5, TRAP	FMN -> RIBOFLAV + PI	3.1.3.2
55	ACPP, PAP	FMN -> RIBOFLAV + PI	3.1.3.2
9.3 Vitamin B6 metabolism PATH:hsa00750			
8566	PDXK, PKH, PNK	PYRDX + ATP -> P5P + ADP	2.7.1.35
		PDLA + ATP -> PDLA5P + ADP	
		PL + ATP -> PL5P + ADP	
9.4 Nicotinate and nicotinamide metabolism PATH:hsa00760			
23475	QPRT	QA + PRPP -> NAMN + CO2 + PPI	2.4.2.19

4837 NNMT		2.1.1.1
683 BST1, CD157	NAD -> NAM + ADPRIB	3.2.2.5
952 CD38	NAD -> NAM + ADPRIB	3.2.2.5
23530 NNT		1.6.1.2
9.5 Pantothenate and CoA biosynthesis PATH:hsa00770		
9.6 Biotin metabolism PATH:hsa00780		
3141 HLCS, HCS		6.3.4.-
		6.3.4.9
		6.3.4.10
		6.3.4.11
		6.3.4.15
686 BTD		3.5.1.12
9.7 Folate biosynthesis PATH:hsa00790		
2643 GCH1, DYT5, GCH, GTPCH1	GTP -> FOR + AHTD	3.5.4.16
1719 DHFR	DHF + NADPH -> NADP + THF	1.5.1.3
2356 FPGS	THF + ATP + GLU <-> ADP + PI + THFG	6.3.2.17
8836 GGH, GH		3.4.19.9
5805 PTS		4.6.1.10
6697 SPR		1.1.1.153
5860 QDPR, DHPR, PKU2	NADPH + DHBP -> NADP + THBP	1.6.99.7
9.8 One carbon pool by folate PATH:hsa00670		
10840 FTHFD		1.5.1.6
10588 MTHFS	ATP + FTHF -> ADP + PI + MTHF	6.3.3.2
9.10 Porphyrin and chlorophyll metabolism PATH:hsa00860		
210 ALAD	2 ALAV -> PBG	4.2.1.24
3145 HMBS, PBGD, UPS	4 PBG -> HMB + 4 NH3	4.3.1.8
7390 UROS	HMB -> UPRG	4.2.1.75
7389 UROD	UPRG -> 4 CO2 + CPP	4.1.1.37
1371 CPO, CPX	O2 + CPP -> 2 CO2 + PPHG	1.3.3.3
5498 PPOX, PPO	O2 + PPHGm -> PPIXm	1.3.3.4
2235 FECH, FCE	PPIXm -> PTHm	4.99.1.1
3162 HMOX1, HO-1		1.14.99.3
3163 HMOX2, HO-2		1.14.99.3
644 BLVRA, BLVR		1.3.1.24
645 BLVRB, FLR		1.3.1.24
		1.6.99.1
2232 FDXR, ADXR		1.18.1.2
3052 HCCS, CCHL		4.4.1.17
1356 CP		1.16.3.1
9.11 Ubiquinone biosynthesis PATH:hsa00130		
4938 OAS1, IFI-4, OIAS		2.7.7.-
4939 OAS2, P69		2.7.7.-
5557 PRIM1		2.7.7.-
5558 PRIM2A, PRIM2		2.7.7.-
5559 PRIM2B, PRIM2		2.7.7.-
7015 TERT, EST2, TCS1, TP2, TRT		2.7.7.-
8638 OASL, TRIP14		2.7.7.-
10. Metabolism of Other Substances		
10.1 Terpenoid biosynthesis PATH:hsa00900		
10.2 Flavonoids, stilbene and lignin biosynthesis PATH:hsa00940		
10.3 Alkaloid biosynthesis I PATH:hsa00950		
10.4 Alkaloid biosynthesis II PATH:hsa00960		
10.6 Streptomycin biosynthesis PATH:hsa00521		
10.7 Erythromycin biosynthesis PATH:hsa00522		
10.8 Tetracycline biosynthesis PATH:hsa00253		
10.14 gamma-Hexachlorocyclohexane degradation PATH:hsa00361		
5444 PON1, ESA, PON		3.1.8.1
		3.1.1.2
5445 PON2		3.1.1.2
		3.1.8.1
10.18 1,2-Dichloroethane degradation PATH:hsa00631		
10.20 Tetrachloroethene degradation PATH:hsa00625		
2052 EPHX1, EPHX, MEH		3.3.2.3
2053 EPHX2		3.3.2.3
10.21 Styrene degradation PATH:hsa00643		
11. Transcription (condensed)		
11.1 RNA polymerase PATH:hsa03020		

11.2 Transcription factors PATH:hsa03022
12. Translation (condensed)
12.1 Ribosome PATH:hsa03010
12.2 Translation factors PATH:hsa03012

1915 EEF1A1, EF1A, ALPHA, EEF-1, EEF1A		3.6.1.48
1917 EEF1A2, EF1A		3.6.1.48
1938 EEF2, EF2, EEF-2		3.6.1.48

12.3 Aminoacyl-tRNA biosynthesis PATH:hsa00970
13. Sorting and Degradation (condensed)
13.1 Protein export PATH:hsa03060

23478 SPC18		3.4.21.89

13.4 Proteasome PATH:hsa03050

5687 PSMA6, IOTA, PROS27		3.4.99.46
5683 PSMA2, HC3, MU, PMSA2, PSC2		3.4.99.46
5685 PSMA4, HC9		3.4.99.46
5688 PSMA7, XAPC7		3.4.99.46
5686 PSMA5, ZETA, PSC5		3.4.99.46
5682 PSMA1, HC2, NU, PROS30		3.4.99.46
5684 PSMA3, HC8		3.4.99.46
5698 PSMB9, LMP2, RING12		3.4.99.46
5695 PSMB7, Z		3.4.99.46
5691 PSMB3, HC10-II		3.4.99.46
5690 PSMB2, HC7-I		3.4.99.46
5693 PSMB5, LMPX, MB1		3.4.99.46
5689 PSMB1, HC5, PMSB1		3.4.99.46
5692 PSMB4, HN3, PROS26		3.4.99.46

14. Replication and Repair
14.1 DNA polymerase PATH:hsa03030
14.2 Replication Complex PATH:hsa03032

23626 SPO11		5.99.1.3
7153 TOP2A, TOP2		5.99.1.3
7155 TOP2B		5.99.1.3
7156 TOP3A, TOP3		5.99.1.2
8940 TOP3B		5.99.1.2

22. Enzyme Complex
22.1 Electron Transport System, Complex I PATH:hsa03100
22.2 Electron Transport System, Complex II PATH:hsa03150
22.3 Electron Transport System, Complex III PATH:hsa03140
22.4 Electron Transport System, Complex IV PATH:hsa03130
22.5 ATP Synthase PATH:hsa03110
22.8 ATPases PATH:hsa03230
23. Unassigned
23.1 Enzymes

5538 PPT1, CLN1, PPT, INCL	C160ACP + H2O -> C160 + ACP	3.1.2.22

23.2 Non-enzymes

22934 RPIA, RPI	RL5P <-> R5P	5.3.1.6
5250 SLC25A3, PHC	PI + H <-> Hm + PIm	
6576	CIT + MALm <-> CITm + MAL	
51166 LOC51166	AADP + AKG -> GLU + KADP	2.6.1.39
5625 PRODH	PRO + FAD -> P5C + FADH2	1.5.3.-
6517 SLC2A4, GLUT4	GLCxt -> GLC	
6513 SLC2A1, GLUT1, GLUT	GLCxt -> GLC	
26275 HIBCH, HIBYL-COA-H	HIBCOAm + H2Om -> HIBm + COAm	3.1.2.4
23305 KIAA0837, ACS2, LACS5, LACS2	C160 + COA + ATP -> AMP + PPI + C160COA	
8611 PPAP2A, PAP-2A	PA + H2O -> DAGLY + PI	
8612 PPAP2C, PAP-2C	PA + H2O -> DAGLY + PI	
8613 PPAP2B, PAP-2B	PA + H2O -> DAGLY + PI	
56994 LOC56994	CDPCHO + DAGLY -> PC + CMP	
10400 PEMT, PEMT2	SAM + PE -> SAH + PMME	
5833 PCYT2, ET	PETHM + CTP -> CDPETN + PPI	
10390 CEPT1	CDPETN + DAGLY <-> CMP + PE	
8394 PIP5K1A	PINS4P + ATP -> D45PI + ADP	
8395 PIP5K1B, STM7, MSS4	PINS4P + ATP -> D45PI + ADP	
8396 PIP5K2B	PINS4P + ATP -> D45PI + ADP	
23396 PIP5K1C, KIAA0589, PIP5K-GAMMA	PINS4P + ATP -> D45PI + ADP	

24. Our own reactions which need to be found in KEGG

	GL3P <-> GL3Pm	
	T3P2 <-> T3P2m	
	PYR <-> PYRm + Hm	
	ADP + ATPm + PI + H -> Hm + ADPm + ATP + PIm	
	AKG + MALm <-> AKGm + MAL	
	ASPm + GLU + H -> Hm + GLUm + ASP	
	GDP + GTPm + PI + H -> Hm + GDPm + GTP + PIm	
	C160Axt + FABP -> C160FP + ALBxt	
	C160FP -> C160 + FABP	
	C180Axt + FABP -> C180FP + ALBxt	
	C180FP -> C180 + FABP	
	C161Axt + FABP -> C161FP + ALBxt	
	C161FP -> C161 + FABP	
	C181Axt + FABP -> C181FP + ALBxt	
	C181FP -> C181 + FABP	
	C182Axt + FABP -> C182FP + ALBxt	
	C182FP -> C182 + FABP	
	C204Axt + FABP -> C204FP + ALBxt	
	C204FP -> C204 + FABP	
	O2xt -> O2	
	O2 <-> O2m	
	ACTACm + SUCCOAm -> SUCCm + AACCOAm	
	3HB -> 3HBm	
	MGCOAm + H2Om -> H3MCOAm	4.2.1.18
	OMVAL -> OMVALm	
	OIVAL -> OIVALm	
	OICAP -> OICAPm	
	C160CAR <-> C160CARm	
	CAR <-> CARm	
	DMMCOAm -> LMMCOAm	5.1.99.1
amino acid metabolism		
	THR -> NH3 + H2O + OBUT	4.2.1.16
	THR + NAD -> CO2 + NADH + AMA	1.1.1.103
	THR + NAD + COA -> NADH + ACCOA + GLY	
	AASA + NAD -> NADH + AADP	1.2.1.31
	FKYN + H2O -> FOR + KYN	3.5.1.9
	CMUSA -> CO2 + AM6SA	4.1.1.45
	AM6SA + NAD -> AMUCO + NADH	1.2.1.32
	AMUCO + NADPH -> KADP + NADP + NH4	1.5.1.-
	CYSS + AKG <-> GLU + SPYR	
	URO + H2O -> 4I5P	4.2.1.49
	4I5P + H2O -> FIGLU	3.5.2.7
	GLU <-> GLUm + Hm	
	ORN + Hm -> ORNm	
	ORN + Hm + CITRm <-> CITR + ORNm	
	GLU + ATP + NADPH -> NADP + ADP + PI + GLUGSAL	
	GLYAm + ATPm -> ADPm + 2PGm	
	AM6SA -> PIC	
	SPYR + H2O -> H2SO3 + PYR	
	P5C <-> GLUGSAL	
fatty acid synthesis		
	MALCOA + ACP <-> MALACP + COA	2.3.1.39
	ACCOA + ACP <-> ACACP + COA	
	ACACP + 4 MALACP + 8 NADPH -> 8 NADP + C100ACP + 4 CO2 + 4 ACP	
	ACACP + 5 MALACP + 10 NADPH -> 10 NADP + C120ACP + 5 CO2 + 5 ACP	
	ACACP + 6 MALACP + 12 NADPH -> 12 NADP + C140ACP + 6 CO2 + 6 ACP	
	ACACP + 6 MALACP + 11 NADPH -> 11 NADP + C141ACP + 6 CO2 + 6 ACP	
	ACACP + 7 MALACP + 14 NADPH -> 14 NADP + C160ACP + 7 CO2 + 7 ACP	
	ACACP + 7 MALACP + 13 NADPH -> 13 NADP + C161ACP + 7 CO2 + 7 ACP	

	ACACP + 8 MALACP + 16 NADPH -> 16 NADP + C180ACP + 8 CO2 + 8 ACP
	ACACP + 8 MALACP + 15 NADPH -> 15 NADP + C181ACP + 8 CO2 + 8 ACP
	ACACP + 8 MALACP + 14 NADPH -> 14 NADP + C182ACP + 8 CO2 + 8 ACP
	C160COA + CAR -> C160CAR + COA
	C160CARm + COAm -> C160COAm + CARm
fatty acid degredation	
	GL3P + 0.017 C100ACP + 0.062 C120ACP + 0.1 C140ACP + 0.27 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> AGL3P + ACP
	TAGLYm + 3 H2Om -> GLm + 3 C160m
Phospholipid metabolism	
	SAM + PMME -> SAH + PDME
	PDME + SAM -> PC + SAH
	PE + SER <-> PS + ETHM
Muscle contraction	
	MYOACT + ATP -> MYOATP + ACTIN
	MYOATP + ACTIN -> MYOADPAC
	MYOADPAC -> ADP + PI + MYOACT + CONTRACT

Table 2

// Homo Sapiens Core Metabolic Network //

// Glycolysis //
-1 GLC -1 ATP +1 G6P +1 ADP 0 HK1
-1 G6P -1 H2O +1 GLC +1 PI 0 G6PC
-1 G6P +1 F6P 0 GPIR
-1 F6P -1 ATP +1 FDP +1 ADP 0 PFKL
-1 FDP -1 H2O +1 F6P +1 PI 0 FBP1
-1 FDP +1 T3P2 +1 T3P1 0 ALDOAR
-1 T3P2 +1 T3P1 0 TPI1R
-1 T3P1 -1 PI -1 NAD +1 NADH +1 13PDG 0 GAPDR
-1 13PDG -1 ADP +1 3PG +1 ATP 0 PGK1R
-1 13PDG +1 23PDG 0 PGAM1
-1 23PDG -1 H2O +1 3PG +1 PI 0 PGAM2
-1 3PG +1 2PG 0 PGAM3R
-1 2PG +1 PEP +1 H2O 0 ENO1R
-1 PEP -1 ADP +1 PYR +1 ATP 0 PKLR
-1 PYRm -1 COAm -1 NADm +1 NADHm +1 CO2m +1 ACCOAm 0 PDHA1
-1 NAD -1 LAC +1 PYR +1 NADH 0 LDHAR
-1 G1P +1 G6P 0 PGM1R

// TCA //
-1 ACCOAm -1 OAm -1 H2Om +1 COAm +1 CITm 0 CS
-1 CIT +1 ICIT 0 ACO1R
-1 CITm +1 ICITm 0 ACO2R
-1 ICIT -1 NADP +1 NADPH +1 CO2 +1 AKG 0 IDH1
-1 ICITm -1 NADPm +1 NADPHm +1 CO2m +1 AKGm 0 IDH2
-1 ICITm -1 NADm +1 CO2m +1 NADHm +1 AKGm 0 IDH3A
-1 AKGm -1 NADm -1 COAm +1 CO2m +1 NADHm +1 SUCCOAm 0 OGDH
-1 GTPm -1 SUCCm -1 COAm +1 GDPm +1 PIm +1 SUCCOAm 0 SUCLG1R
-1 ATPm -1 SUCCm -1 COAm +1 ADPm +1 PIm +1 SUCCOAm 0 SUCLA2R
-1 FUMm -1 H2Om +1 MALm 0 FHR
-1 MAL -1 NAD +1 NADH +1 OA 0 MDH1R
-1 MALm -1 NADm +1 NADHm +1 OAm 0 MDH2R
-1 PYRm -1 ATPm -1 CO2m +1 ADPm +1 OAm +1 PIm 0 PC
-1 OA -1 GTP +1 PEP +1 GDP +1 CO2 0 PCK1
-1 OAm -1 GTPm +1 PEPm +1 GDPm +1 CO2m 0 PCK2
-1 ATP -1 CIT -1 COA -1 H2O +1 ADP +1 PI +1 ACCOA +1 OA 0 ACLY

```
// PPP //
-1 G6P -1 NADP +1 D6PGL +1 NADPH  0 G6PDR
-1 D6PGL -1 H2O +1 D6PGC  0 PGLS
-1 D6PGC -1 NADP +1 NADPH +1 CO2 +1 RL5P  0 PGD
-1 RL5P +1 X5P  0 RPER
-1 R5P -1 X5P +1 T3P1 +1 S7P  0 TKT1R
-1 X5P -1 E4P +1 F6P +1 T3P1  0 TKT2R
-1 T3P1 -1 S7P +1 E4P +1 F6P  0 TALDO1R
-1 RL5P +1 R5P  0 RPIAR

// Glycogen //
-1 G1P -1 UTP +1 UDPG +1 PPI  0 UGP1
-1 UDPG +1 UDP +1 GLYCOGEN  0 GYS1
-1 GLYCOGEN -1 PI +1 G1P  0 GBE1

// ETS //
-1 MALm -1 NADPm +1 CO2m +1 NADPHm +1 PYRm  0 ME3
-1 MALm -1 NADm +1 CO2m +1 NADHm +1 PYRm  0 ME2
-1 MAL -1 NADP +1 CO2 +1 NADPH +1 PYR  0 ME1
-1 NADHm -1 Qm -4 Hm +1 QH2m +1 NADm +4 H 0 MTND1
-1 SUCCm -1 FADm +1 FUMm +1 FADH2m  0 SDHC1R
-1 FADH2m -1 Qm +1 FADm +1 QH2m 0 SDHC2R
-1 O2m -4 FEROm -4 Hm +4 FERIm +2 H2Om +4 H 0 UQCRFS1
-1 QH2m -2 FERIm -4 Hm +1 Qm +2 FEROm +4 H 0 COX5BL4
-1 ADPm -1 PIm -3 H +1 ATPm +3 Hm +1 H2Om 0 MTAT
-1 ADP -1 ATPm -1 PI -1 H +1 Hm +1 ADPm +1 ATP +1 PIm  0 ATPMC
-1 GDP -1 GTPm -1 PI -1 H +1 Hm +1 GDPm +1 GTP +1 PIm  0 GTPMC
-1 PPI +2 PI  0 PP

-1 ACCOA -1 ATP -1 CO2 +1 MALCOA +1 ADP +1 PI  0 ACACAR
-1 GDP -1 ATP +1 GTP +1 ADP  0 GOT3R


// Transporters //
-1 CIT -1 MALm +1 CITm +1 MAL  0 CITMCR
-1 PYR -1 H +1 PYRm +1 Hm  0 PYRMCR

// Glycerol Phosphate Shuttle //
-1 GL3Pm -1 FADm +1 T3P2m +1 FADH2m  0 GPD2
-1 T3P2 -1 NADH +1 GL3P +1 NAD  0 GPD1
-1 GL3P +1 GL3Pm  0 GL3PMCR
-1 T3P2 +1 T3P2m  0 T3P2MCR

// Malate/Aspartate Shuttle //
-1 OAm -1 GLUm +1 ASPm +1 AKGm  0 GOT1R
-1 ASP -1 AKG +1 OA +1 GLU  0 GOT2R
-1 AKG -1 MALm +1 AKGm +1 MAL  0 MALMCR
-1 ASPm -1 GLU -1 H +1 Hm +1 GLUm +1 ASP  0 ASPMC
```

```
// Exchange Fluxes //
+1 GLC 0 GLCexR
+1 PYR 0 PYRexR
+1 CO2 0 CO2exR
+1 O2  0 O2exR
+1 PI  0 PIexR
+1 H2O 0 H2OexR
+1 LAC 0 LACexR

+1 CO2m 0 CO2min
-1 CO2m 0 CO2mout
+1 O2m 0 O2min
-1 O2m  0 O2mout
+1 H2Om 0 H2Omin
-1 H2Om 0 H2Omout
+1 PIm  0 PImin
-1 PIm  0 PImout


// Output //
-1 ATP +1 ADP +1 PI 0 Output

0.0 end

end E 0

max
1 Output
0 end

0 GLCexR 1
-1000 PYRexR 0
-1000 LACexR 0

0 end 0
rev. rxn 33
nonrev. rxn 31
total rxn 64
matrix columns 97
unique enzymes 52
```

Table 3

Abbrev.	Reaction	Rxn Name
Glycolysis		
HK1	GLC + ATP -> G6P + ADP	HK1
G6PC, G6PT	G6P + H2O -> GLC + PI	G6PC
GPI	G6P <-> F6P	GPI
PFKL	F6P + ATP -> FDP + ADP	PFKL
FBP1, FBP	FDP + H2O -> F6P + PI	FBP1
ALDOA	FDP <-> T3P2 + T3P1	ALDOA
TPI1	T3P2 <-> T3P1	TPI1
GAPD, GAPDH	T3P1 + PI + NAD <-> NADH + 13PDG	GAPD
PGK1, PGKA	13PDG + ADP <-> 3PG + ATP	PGK1
PGAM1, PGAMA	13PDG <-> 23PDG	PGAM1
	23PDG + H2O -> 3PG + PI	PGAM2
	3PG <-> 2PG	PGAM3
ENO1, PPH, ENO1L1	2PG <-> PEP + H2O	ENO1
PKLR, PK1	PEP + ADP -> PYR + ATP	PKLR
PDHA1, PHE1A, PDHA	PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	PDHA1
LDHA, LDH1	NAD + LAC <-> PYR + NADH	LDHA
PGM1	G1P <-> G6P	PGM1
TCA		
CS	ACCOAm + OAm + H2Om -> COAm + CITm	CS
ACO1, IREB1, IRP1	CIT <-> ICIT	ACO1
ACO2	CITm <-> ICITm	ACO2
IDH1	ICIT + NADP -> NADPH + CO2 + AKG	IDH1
IDH2	ICITm + NADPm -> NADPHm + CO2m + AKGm	IDH2
IDH3A	ICITm + NADm -> CO2m + NADHm + AKGm	IDH3A
OGDH	AKGm + NADm + COAm -> CO2m + NADHm + SUCCOAm	OGDH
SUCLG1, SUCLA1	GTPm + SUCCm + COAm <-> GDPm + PIm + SUCCOAm	SUCLG1
SUCLA2	ATPm + SUCCm + COAm <-> ADPm + PIm + SUCCOAm	SUCLA2
FH	FUMm + H2Om <-> MALm	FH
MDH1	MAL + NAD <-> NADH + OA	MDH1
MDH2	MALm + NADm <-> NADHm + OAm	MDH2
PC, PCB	PYRm + ATPm + CO2m -> ADPm + OAm + PIm	PC
ACLY, ATPCL, CLATP	ATP + CIT + COA + H2O -> ADP + PI + ACCOA + OA	ACLY
PCK1	OA + GTP -> PEP + GDP + CO2	PCK1
PPP		
G6PD, G6PD1	G6P + NADP <-> D6PGL + NADPH	G6PD
PGLS, 6PGL	D6PGL + H2O -> D6PGC	PGLS
PGD	D6PGC + NADP -> NADPH + CO2 + RL5P	PGD
RPE	RL5P <-> X5P	RPE
TKT	R5P + X5P <-> T3P1 + S7P	TKT1
	X5P + E4P <-> F6P + T3P1	TKT2
TALDO1	T3P1 + S7P <-> E4P + F6P	TALDO1
UGP1	G1P + UTP -> UDPG + PPI	UGP1
ACACA, ACAC, ACC	ACCOA + ATP + CO2 <-> MALCOA + ADP + PI + H	ACACA
ETS		
ME3	MALm + NADPm -> CO2m + NADPHm + PYRm	ME3
MTND1	NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	MTND1
SDHC	SUCCm + FADm <-> FUMm + FADH2m	SDHC1
	FADH2m + Qm <-> FADm + QH2m	SDHC2
UQCRFS1, RIS1	O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	UQCRFS1
COX5BL4	QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	COX5BL4
MTATP6	ADPm + PIm + 3 H -> ATPm + 3 Hm + H2Om	MTAT
PP, SID6-8061	PPI -> 2 PI	PP
Malate Aspartate shunttle		
GOT1	OAm + GLUm <-> ASPm + AKGm	GOT1
GOT2	OA + GLU <-> ASP + AKG	GOT2
	GDP + ATP <-> GTP + ADP	GOT3

Glycogen		
GBE1	GLYCOGEN + PI -> G1P	GBE1
GYS1, GYS	UDPG -> UDP + GLYCOGEN	GYS1
Glycerol Phosphate Shunttle		
GPD2	GL3Pm + FADm -> T3P2m + FADH2m	GPD2
GPD1	T3P2 + NADH -> GL3P + NAD	GPD1
RPIA, RPI	RL5P <-> R5P	RPIA
Mitochondria Transport		
	CIT + MALm <-> C[Tm + MAL	CITMC
	GL3P <-> GL3Pm	GL3PMC
	T3P2 <-> T3P2m	T3P2MC
	PYR <-> PYRm + Hm	PYRMC
	ADP + ATPm + PI + H -> Hm + ADPm + ATP + PIm	ATPMC
	AKG + MALm <-> AKGm + MAL	MALMC
	ASPm + GLU + H -> Hm + GLUm + ASP	ASPMC
	GDP + GTPm + PI + H -> Hm + GDPm + GTP + PIm	GTPMC

TABLE 4
Metabolic Reaction for Muscle Cells

Reaction		*Rxt Name*
GLC + ATP -> G6P + ADP	0	HK1
G6P <-> F6P	0	GPI
F6P + ATP -> FDP + ADP	0	PFKL1
FDP + H2O -> F6P + PI	0	FBP1
FDP <-> T3P2 + T3P1	0	ALDOA
T3P2 <-> T3P1	0	TPI1
T3P1 + PI + NAD <-> NADH + 13PDG	0	GAPD
13PDG + ADP <-> 3PG + ATP	0	PGK1
3PG <-> 2PG	0	PGAM3
2PG <-> PEP + H2O	0	ENO1
PEP + ADP -> PYR + ATP	0	PK1
PYRm + COAm + NADm -> + NADHm + CO2m + ACCOAm	0	PDHA1
NAD + LAC <-> PYR + NADH	0	LDHA
G1P <-> G6P	0	PGM1
ACCOAm + OAm + H2Om -> COAm + CITm	0	CS
CIT <-> ICIT	0	ACO1
CITm <-> ICITm	0	ACO2
ICIT + NADP -> NADPH + CO2 + AKG	0	IDH1
ICITm + NADPm -> NADPHm + CO2m + AKGm	0	IDH2
ICITm + NADm -> CO2m + NADHm + AKGm	0	IDH3A
AKGm + NADm + COAm -> CO2m + NADHm + SUCCOAm	0	OGDH
GTPm + SUCCm + COAm <-> GDPm + PIm + SUCCOAm	0	SUCLG1
ATPm + SUCCm + COAm <-> ADPm + PIm + SUCCOAm	0	SUCLA2
FUMm + H2Om <-> MALm	0	FH
MAL + NAD <-> NADH + OA	0	MDH1
MALm + NADm <-> NADHm + OAm	0	MDH2
PYRm + ATPm + CO2m -> ADPm + OAm + PIm	0	PC
ATP + CIT + COA + H2O -> ADP + PI + ACCOA + OA	0	ACLY
OA + GTP -> PEP + GDP + CO2	0	PCK1
OAm + GTPm -> PEPm + GDPm + CO2m	0	PCK2
G6P + NADP <-> D6PGL + NADPH	0	G6PD
D6PGL + H2O -> D6PGC	0	H6PD
D6PGC + NADP -> NADPH + CO2 + RL5P	0	PGD
RL5P <-> X5P	0	RPE
R5P + X5P <-> T3P1 + S7P	0	TKT1
X5P + E4P <-> F6P + T3P1	0	TKT2
T3P1 + S7P <-> E4P + F6P	0	TALDO1
RL5P <-> R5P	0	RPIA
G1P + UTP -> UDPG + PPI	0	UGP1
GLYCOGEN + PI -> G1P	0	GBE1
UDPG -> UDP + GLYCOGEN	0	GYS1
MALm + NADm -> CO2m + NADHm + PYRm	0	ME2
MALm + NADPm -> CO2m + NADPHm + PYRm	0	ME3
MAL + NADP -> CO2 + NADPH + PYR	0	HUMNDME
NADHm + Qm + 4 Hm -> QH2m + NADm + 4 H	0	MTND1
SUCCm + FADm <-> FUMm + FADH2m	0	SDHC1
FADH2m + Qm <-> FADm + QH2m	0	SDHC2
O2m + 4 FEROm + 4 Hm -> 4 FERIm + 2 H2Om + 4 H	0	UQCRFS1
QH2m + 2 FERIm + 4 Hm -> Qm + 2 FEROm + 4 H	0	COX5BL4
ADPm + PIm + 3 H -> ATPm + 3 Hm + H2Om	0	MTAT1
ADP + ATPm + PI + H -> Hm + ADPm + ATP + PIm	0	ATPMC
GDP + GTPm + PI + H -> Hm + GDPm + GTP + PIm	0	GTPMC
PPI -> 2 PI	0	PP
GDP + ATP <-> GTP + ADP	0	NME1
ACCOA + ATP + CO2 <-> MALCOA + ADP + PI + H	0	ACACA
MALCOA + ACP <-> MALACP + COA	0	FAS1_1
ACCOA + ACP <-> ACACP + COA	0	FAS1_2
ACACP + 4 MALACP + 8 NADPH -> 8 NADP + C100ACP + 4 CO2 + 4 ACP	0	C100SY
ACACP + 5 MALACP + 10 NADPH -> 10 NADP + C120ACP + 5 CO2 + 5 ACP	0	C120SY
ACACP + 6 MALACP + 12 NADPH -> 12 NADP + C140ACP + 6 CO2 + 6 ACP	0	C140SY
ACACP + 6 MALACP + 11 NADPH -> 11 NADP + C141ACP + 6 CO2 + 6 ACP	0	C141SY
ACACP + 7 MALACP + 14 NADPH -> 14 NADP + C160ACP + 7 CO2 + 7 ACP	0	C160SY
ACACP + 7 MALACP + 13 NADPH -> 13 NADP + C161ACP + 7 CO2 + 7 ACP	0	C161SY
ACACP + 8 MALACP + 16 NADPH -> 16 NADP + C180ACP + 8 CO2 + 8 ACP	0	C180SY
ACACP + 8 MALACP + 15 NADPH -> 15 NADP + C181ACP + 8 CO2 + 8 ACP	0	C181SY
ACACP + 8 MALACP + 14 NADPH -> 14 NADP + C182ACP + 8 CO2 + 8 ACP	0	C182SY
C160ACP + H2O -> C160 + ACP	0	PPT1
C160 + COA + ATP -> AMP + PPI + C160COA	0	KIAA

C160COA + CAR -> C160CAR + COA	0 C160CA
C160CARm + COAm -> C160COAm + CARm	0 C160CB
C160CARm + COAm + FADm + NADm -> FADH2m + NADHm + C140COAm + ACCOAm	0 HADHA
C140COAm + 7 COAm + 7 FADm + 7 NADm -> 7 FADH2m + 7 NADHm + 7 ACCOAm	0 HADH2
TAGLYm + 3 H2Om -> GLm + 3 C160m	0 TAGRXN
GL3P + 0.017 C100ACP + 0.062 C120ACP + 0.1 C140ACP + 0.27 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> AGL3P + ACP	0 GAT1
AGL3P + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> PA + ACP	0 AGPAT1
ATP + CHO -> ADP + PCHO	0 CHKL1
PCHO + CTP -> CDPCHO + PPI	0 PCYT1A
CDPCHO + DAGLY -> PC + CMP	0 LOC
SAM + PE -> SAH + PMME	0 PEMT
SAM + PMME -> SAH + PDME	0 MFPS
PDME + SAM -> PC + SAH	0 PNMNM
G6P -> MI1P	0 ISYNA1
MI1P -> MYOI + PI	0 IMPA1
PA + CTP <-> CDPDG + PPI	0 CDS1
CDPDG + MYOI -> CMP + PINS	0 PIS
ATP + PINS -> ADP + PINSP	0 PIK3CA
ATP + PINS -> ADP + PINS4P	0 PIK4CA
PINS4P + ATP -> D45PI + ADP	0 PIP5K1
D45PI -> TPI + DAGLY	0 PLCB2
PA + H2O -> DAGLY + PI	0 PPAP2A
DAGLY + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP -> TAGLY + ACP	0 DGAT
CDPDG + SER <-> CMP + PS	0 PTDS
CDPETN + DAGLY <-> CMP + PE	0 CEPT1
PE + SER <-> PS + ETHM	0 PESER
ATP + ETHM -> ADP + PETHM	0 EKI1
PETHM + CTP -> CDPETN + PPI	0 PCYT2
PS -> PE + CO2	0 PISD
3HBm + NADm -> NADHm + Hm + ACTACm	0 BDH
ACTACm + SUCCOAm -> SUCCm + AACOAm	0 3OCT
THF + SER <-> GLY + METTHF	0 SHMT1
THFm + SERm <-> GLYm + METTHFm	0 SHMT2
SERm + PYRm <-> ALAm + 3HPm	0 AGXT
3PG + NAD <-> NADH + PHP	0 PHGDH
PHP + GLU <-> AKG + 3PSER	0 PSA
3PSER + H2O -> PI + SER	0 PSPH
3HPm + NADHm -> NADm + GLYAm	0 GLYD
SER -> PYR + NH3 + H2O	0 SDS
GLYAm + ATPm -> ADPm + 2PGm	0 GLTK
PYR + GLU <-> AKG + ALA	0 GPT
GLUm + CO2m + 2 ATPm -> 2 ADPm + 2 PIm + CAPm	0 CPS1
AKGm + NADHm + NH3m <-> NADm + H2Om + GLUm	0 GLUD1
AKGm + NADPHm + NH3m <-> NADPm + H2Om + GLUm	0 GLUD2
GLUm + NH3m + ATPm -> GLNm + ADPm + PIm	0 GLUL
ASPm + ATPm + GLNm -> GLUm + ASNm + AMPm + PPIm	0 ASNS
ORN + AKG <-> GLUGSAL + GLU	0 OAT
GLU <-> GLUm + Hm	0 GLUMT
GLU + ATP + NADPH -> NADP + ADP + PI + GLUGSAL	0 P5CS
GLUP + NADH -> NAD + PI + GLUGSAL	0 PYCS
P5C <-> GLUGSAL	0 SPTC
HIS -> NH3 + URO	0 HAL
URO + H2O -> 4I5P	0 UROH
4I5P + H2O -> FIGLU	0 IMPR
FIGLU + THF -> NFTHF + GLU	0 FTCD
MET + ATP + H2O -> PPI + PI + SAM	0 MAT1A
SAM + DNA -> SAH + DNA5MC	0 DNMT1
SAH + H2O -> HCYS + ADN	0 AHCYL1
HCYS + MTHF -> THF + MET	0 MTR
SER + HCYS -> LLCT + H2O	0 CBS
LLCT + H2O -> CYS + HSER	0 CTH1
OBUT + NH3 <-> HSER	0 CTH2
CYS + O2 <-> CYSS	0 CDO1
CYSS + AKG <-> GLU + SPYR	0 CYSAT
SPYR + H2O -> H2SO3 + PYR	0 SPTB
LYS + NADPH + AKG -> NADP + H2O + SAC	0 LKR1
SAC + H2O + NAD -> GLU + NADH + AASA	0 LKR2
AASA + NAD -> NADH + AADP	0 2ASD
AADP + AKG -> GLU + KADP	0 LOC5
TRP + O2 -> FKYN	0 TDO2
FKYN + H2O -> FOR + KYN	0 KYNF
KYN + NADPH + O2 -> HKYN + NADP + H2O	0 KMO
HKYN + H2O -> HAN + ALA	0 KYNU2

HAN + O2 -> CMUSA	0 HAAO
CMUSA -> CO2 + AM6SA	0 ACSD
AM6SA -> PIC	0 SPTA
AM6SA + NAD -> AMUCO + NADH	0 AMSD
AMUCO + NADPH -> KADP + NADP + NH4	0 2AMR
ARG -> ORN + UREA	0 ARG2
ORN + Hm -> ORNm	0 ORNMT
ORN + Hm + CITRm <-> CITR + ORNm	0 ORNCITT
ORNm + CAPm -> CITRm + Pim + Hm	0 OTC
CITR + ASP + ATP <-> AMP + PPI + ARGSUCC	0 ASS
ARGSUCC -> FUM + ARG	0 ASL
PRO + FAD -> P5C + FADH2	0 PRODH
P5C + NADPH -> PRO + NADP	0 PYCR1
THR -> NH3 + H2O + OBUT	0 WTDH
THR + NAD -> CO2 + NADH + AMA	0 TDH
AMA + H2O + FAD -> NH3 + FADH2 + MTHGXL	0 MAOA
GLYm + THFm + NADm <-> METTHFm + NADHm + CO2m + NH3m	0 AMT
PHE + THBP + O2 -> TYR + DHBP + H2O	0 PAH
NADPH + DHBP -> NADP + THBP	0 QDPR
AKG + TYR -> HPHPYR + GLU	0 TAT
HPHPYR + O2 -> HGTS + CO2	0 HPD
HGTS + O2 -> MACA	0 HGD
MACA -> FACA	0 GSTZ1
FACA + H2O -> FUM + ACA	0 FAH
AKG + ILE -> OMVAL + GLU	0 BCAT1A
OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m	0 BCKDHAA
MBCOAm + FADm -> MCCOAm + FADH2m	0 ACADMA
MCCOAm + H2Om -> MHVCOAm	0 ECHS1B
MHVCOAm + NADm -> MAACOAm + NADHm	0 EHHADHA
MAACOAm -> ACCOAm + PROPCOAm	0 ACAA2
2 ACCOAm <-> COAm + AACCOAm	0 ACATm1
AKG + VAL -> OIVAL + GLU	0 BCAT1B
OIVALm + COAm + NADm -> IBCOAm + NADHm + CO2m	0 BCKDHAB
IBCOAm + FADm -> MACOAm + FADH2m	0 ACADSB
MACOAm + H2Om -> HIBCOAm	0 EHHADHC
HIBCOAm + H2Om -> HIBm + COAm	0 HIBCHA
HIBm + NADm -> MMAm + NADHm	0 EHHADHB
MMAm + COAm + NADm -> NADHm + CO2m + PROPCOAm	0 MMSDH
PROPCOAm + CO2m + ATPm -> ADPm + PIm + DMMCOAm	0 PCCA
DMMCOAm -> LMMCOAm	0 HIBCHF
LMMCOAm -> SUCCOAm	0 MUT
AKG + LEU -> OICAP + GLU	0 BCAT1C
OICAPm + COAm + NADm -> IVCOAm + NADHm + CO2m	0 BCKDHAC
OICAPm + COAm + NADH -> IVCOAm + NADHm + CO2m	0 BCKDHBC
OICAPm + COAm + NADHm -> IVCOAm + NADHm + CO2m	0 DBTC
IVCOAm + FADm -> MCRCOAm + FADH2m	0 IVD
MCRCOAm + ATPm + CO2m + H2Om -> MGCOAm + ADPm + Pim	0 MCCC1
MGCOAm + H2Om -> H3MCOAm	0 HIBCHB
H3MCOAm -> ACCOAm + ACTACm	0 HMGCL
MYOACT + ATP -> MYOATP + ACTIN	0 MYOSA
MYOATP + ACTIN -> MYOADPAC	0 MYOSB
MYOADPAC -> ADP + PI + MYOACT + CONTRACT	0 MYOSC
PCRE + ADP -> CRE + ATP	0 CREATA
AMP + H2O -> PI + ADN	0 CREATB
ATP + AMP <-> 2 ADP	0 CREATC
O2 <-> O2m	0 O2MT
3HB -> 3HBm	0 HBMT
CIT + MALm <-> CITm + MAL	0 CITMC
PYR <-> PYRm + Hm	0 PYRMC
C160CAR + COAm -> C160COAm + CAR	0 C160CM
OMVAL -> OMVALm	0 HIBCHC
OIVAL -> OIVALm	0 HIBCHD
OICAP -> OICAPm	0 HIBCHE
GL <-> GLm	0 GLMT
GL3Pm + FADm -> T3P2m + FADH2m	0 GPD2
T3P2 + NADH <-> GL3P + NAD	0 GPD1
GL3P <-> GL3Pm	0 GL3PMC
T3P2 <-> T3P2m	0 T3P2MC
OAm + GLUm <-> ASPm + AKGm	0 GOT1
OA + GLU <-> ASP + AKG	0 GOT2
AKG + MALm <-> AKGm + MAL	0 MALMC
ASPm + GLU + H -> Hm + GLUm + ASP	0 ASPMC
GLCxt -> GLC	0 GLUT4
O2xt -> O2	0 O2UP
C160Axt + FABP -> C160FP + ALBxt	0 FAT1
C160FP -> C160 + FABP	0 FAT2
C180Axt + FABP -> C180FP + ALBxt	0 FAT3
C180FP -> C180 + FABP	0 FAT4
C161Axt + FABP -> C161FP + ALBxt	0 FAT5
C161FP -> C161 + FABP	0 FAT6
C181Axt + FABP -> C181FP + ALBxt	0 FAT7

C181FP -> C181 + FABP	0 FAT8
C182Axt + FABP -> C182FP + ALBxt	0 FAT9
C182FP -> C182 + FABP	0 FAT10
C204Axt + FABP -> C204FP + ALBxt	0 FAT11
C204FP -> C204 + FABP	0 FAT12
PYRxt + HEXT <-> PYR + H	0 PYRUP
LACxt + HEXT <-> LAC + HEXT	0 LACUP
H <-> HEXT	0 HextUP
CO2 <-> CO2m	0 CO2MT
H2O <-> H2Om	0 H2OMT
ATP + AC + COA -> AMP + PPI + ACCOA	0 FLJ2
C160CAR <-> C160CARm	0 C160MT
CARm <-> CAR	0 CARMT
CO2xt <-> CO2	0 CO2UP
H2Oxt <-> H2O	0 H2OUP
PIxt + HEXT <-> HEXT + PI	0 PIUP
<-> GLCxt	0 GLCexR
<-> PYRxt	0 PYRexR
<-> CO2xt	0 CO2exR
<-> O2xt	0 O2exR
<-> PIxt	0 PIexR
<-> H2Oxt	0 H2OexR
<-> LACxt	0 LACexR
<-> C160Axt	0 C160AexR
<-> C161Axt	0 C161AexR
<-> C180Axt	0 C180AexR
<-> C181Axt	0 C181AexR
<-> C182Axt	0 C182AexR
<-> C204Axt	0 C204AexR
<-> ALBxt	0 ALBexR
<-> 3HB	0 HBexR
<-> GLYCOGEN	0 GLYex
<-> PCRE	0 PCREex
<-> TAGLYm	0 TAGmex
<-> ILE	0 ILEex
<-> VAL	0 VALex
<-> CRE	0 CREex
<-> ADN	0 ADNex
<-> PI	0 PIex

What is claimed is:

1. A computer readable medium or media, comprising:

(a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product,

wherein at least one of said *Homo sapiens* reactions is annotated to indicate an associated gene;

(b) a gene database comprising information characterizing said associated gene;

(c) a constraint set for said plurality of *Homo sapiens* reactions, and

(d) commands for determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data representation, wherein said at least one flux distribution is predictive of a *Homo sapiens* physiological function.

2. The computer readable medium or media of claim 1, wherein said plurality of *Homo sapiens* reactions comprises at least one reaction from a peripheral metabolic pathway.

3. The computer readable medium or media of

claim 2, wherein said peripheral metabolic pathway is selected from the group consisting of amino acid biosynthesis, amino acid degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, cofactor biosynthesis and transport processes.

4. The computer readable medium or media of claim 1, wherein said *Homo sapiens* physiological function is selected from the group consisting of growth, energy production, redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor, transport of a metabolite, and consumption of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen.

5. The computer readable medium or media of claim 1, wherein said *Homo sapiens* physiological function is selected from the group consisting of degradation of a protein, degradation of an amino acid, degradation of a purine, degradation of a pyrimidine, degradation of a lipid, degradation of a fatty acid and degradation of a cofactor.

6. The computer readable medium or media of claim 1, wherein said data structure comprises a set of linear algebraic equations.

7. The computer readable medium or media of claim 1, wherein said data structure comprises a matrix.

8. The computer readable medium or media of claim 1, wherein said commands comprise an optimization problem.

9. The computer readable medium or media of claim 1, wherein said commands comprise a linear program.

10. The computer readable medium or media of claim 1, wherein at least one reactant in said plurality of *Homo sapiens* reactants or at least one reaction in said plurality of *Homo sapiens* reactions is annotated with an assignment to a subsystem or compartment.

11. The computer readable medium or media of claim 10, wherein a first substrate or product in said plurality of *Homo sapiens* reactions is assigned to a first compartment and a second substrate or product in said plurality of *Homo sapiens* reactions is assigned to a second compartment.

12. The computer readable medium or media of claim 1, wherein a plurality of said *Homo sapiens* reactions is annotated to indicate a plurality of associated genes and wherein said gene database comprises information characterizing said plurality of associated genes.

13. A computer readable medium or media, comprising:

(a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product,

wherein at least one of said *Homo sapiens* reactions is a regulated reaction;

(b) a constraint set for said plurality of *Homo sapiens* reactions, wherein said constraint set includes a variable constraint for said regulated reaction, and

(c) commands for determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data representation, wherein said at least one flux distribution is predictive of a *Homo sapiens* physiological function.

14. The computer readable medium or media of claim 13, wherein said variable constraint is dependent upon the outcome of at least one reaction in said data structure.

15. The computer readable medium or media of claim 13, wherein said variable constraint is dependent upon the outcome of a regulatory event.

16. The computer readable medium or media of claim 13, wherein said variable constraint is dependent upon time.

17. The computer readable medium or media of

claim 13, wherein said variable constraint is dependent upon the presence of a biochemical reaction network participant.

18. The computer readable medium or media of claim 17, wherein said participant is selected from the group consisting of a substrate, product, reaction, protein, macromolecule, enzyme and gene.

19. The computer readable medium or media of claim 13, wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise variable constraints.

20. A computer readable medium or media, comprising:

(a) a data structure relating a plurality of *Homo sapiens* skeletal muscle cell reactants to a plurality of *Homo sapiens* skeletal muscle cell reactions, wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

(b) a constraint set for said plurality of *Homo sapiens* reactions, and

(c) commands for determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data representation, wherein said at least one flux distribution is predictive of *Homo sapiens* skeletal muscle cell energy production.

21. A method for predicting a *Homo sapiens* physiological function, comprising:

(a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product,

wherein at least one of said *Homo sapiens* reactions is annotated to indicate an associated gene;

(b) providing a constraint set for said plurality of *Homo sapiens* reactions;

(c) providing an objective function, and

(d) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby predicting a *Homo sapiens* physiological function related to said gene.

22. The method of claim 21, wherein said plurality of *Homo sapiens* reactions comprises at least one reaction from a peripheral metabolic pathway.

23. The method of claim 22, wherein said peripheral metabolic pathway is selected from the group consisting of amino acid biosynthesis, amino acid degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, cofactor biosynthesis and transport processes.

24. The method of claim 21, wherein said *Homo sapiens* physiological function is selected from the group consisting of growth, energy production,

redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor, transport of a metabolite, and consumption of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen.

25. The method of claim 21, wherein said *Homo sapiens* physiological function is selected from the group consisting of glycolysis, the TCA cycle, pentose phosphate pathway, respiration, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, transport of a metabolite and metabolism of a carbon source, nitrogen source, oxygen source, phosphate source, hydrogen source or sulfur source.

26. The method of claim 21, wherein said data structure comprises a set of linear algebraic equations.

27. The method of claim 21, wherein said data structure comprises a matrix.

28. The method of claim 21, wherein said flux distribution is determined by linear programming.

29. The method of claim 21, further comprising:

(e) providing a modified data structure, wherein said modified data structure comprises at least one added reaction, compared to the data structure of part (a), and

(f) determining at least one flux distribution

that minimizes or maximizes said objective function when said constraint set is applied to said modified data structure, thereby predicting a *Homo sapiens* physiological function.

30. The method of claim 29, further comprising

identifying at least one participant in said at least one added reaction.

31. The method of claim 30, wherein said identifying at least one participant comprises associating a *Homo sapiens* protein with said at least one reaction.

32. The method of claim 31, further comprising

identifying at least one gene that encodes said protein.

33. The method of claim 30, further comprising

identifying at least one compound that alters the activity or amount of said at least one participant, thereby identifying a candidate drug or agent that alters a *Homo sapiens* physiological function.

34. The method of claim 21, further comprising:

(e) providing a modified data structure, wherein said modified data structure lacks at least one reaction compared to the data structure of part (a), and

(f) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said modified data structure, thereby predicting a *Homo sapiens* physiological function.

35. The method of claim 34, further comprising identifying at least one participant in said at least one reaction.

36. The method of claim 35, wherein said identifying at least one participant comprises associating a *Homo sapiens* protein with said at least one reaction.

37. The method of claim 36, further comprising identifying at least one gene that encodes said protein that performs said at least one reaction.

38. The method of claim 35, further comprising identifying at least one compound that alters the activity or amount of said at least one participant, thereby identifying a candidate drug or agent that alters a *Homo sapiens* physiological function.

39. The method of claim 21, further comprising:

(e) providing a modified constraint set, wherein said modified constraint set comprises a changed constraint for at least one reaction compared to the constraint for said at least one reaction in the data structure of part (a), and

(f) determining at least one flux distribution

that minimizes or maximizes said objective function when said modified constraint set is applied to said data structure, thereby predicting a *Homo sapiens* physiological function.

40. The method of claim 39, further comprising

identifying at least one participant in said at least one reaction.

41. The method of claim 40, wherein said identifying at least one participant comprises associating a *Homo sapiens* protein with said at least one reaction.

42. The method of claim 41, further comprising

identifying at least one gene that encodes said protein.

43. The method of claim 40, further comprising

identifying at least one compound that alters the activity or amount of said at least one participant, thereby identifying a candidate drug or agent that alters a *Homo sapiens* physiological function.

44. The method of claim 21, further comprising

providing a gene database relating one or more reactions in said data structure with one or more genes or proteins in *Homo sapiens*.

45. A method for predicting a *Homo sapiens* physiological function, comprising:

(a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product,

wherein at least one of said *Homo sapiens* reactions is a regulated reaction;

(b) providing a constraint set for said plurality of *Homo sapiens* reactions, wherein said constraint set includes a variable constraint for said regulated reaction;

(c) providing a condition-dependent value to said variable constraint;

(d) providing an objective function, and

(e) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby predicting a *Homo sapiens* physiological function.

46. The method of claim 45, wherein said value

provided to said variable constraint changes in response to the outcome of at least one reaction in said data structure.

47. The method of claim 45, wherein said value provided to said variable constraint changes in response to the outcome of a regulatory event.

48. The method of claim 45, wherein said value provided to said variable constraint changes in response to time.

49. The method of claim 45, wherein said value provided to said variable constraint changes in response to the presence of a biochemical reaction network participant.

50. The method of claim 49, wherein said participant is selected from the group consisting of a substrate, product, reaction, enzyme, protein, macromolecule and gene.

51. The method of claim 45, wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise variable constraints.

52. A method for predicting *Homo sapiens* growth, comprising:

(a) providing a data structure relating a plurality of *Homo sapiens* skeletal muscle cell reactants to a plurality of *Homo sapiens* skeletal muscle cell reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

(b) providing a constraint set for said plurality of *Homo sapiens* reactions;

(c) providing an objective function, and

(d) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby predicting *Homo sapiens* skeletal muscle cell energy production.

53. A method for making a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions in a computer readable medium or media, comprising:

(a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of said *Homo sapiens* reactions;

(b) relating said plurality of *Homo sapiens* reactants to said plurality of *Homo sapiens* reactions in a data structure,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

(c) determining a constraint set for said plurality of *Homo sapiens* reactions;

(d) providing an objective function;

(e) determining at least one flux distribution that minimizes or maximizes said objective

function when said constraint set is applied to said data structure, and

(f) if said at least one flux distribution is not predictive of a *Homo sapiens* physiological function, then adding a reaction to or deleting a reaction from said data structure and repeating step (e),

if said at least one flux distribution is predictive of a *Homo sapiens* physiological function, then storing said data structure in a computer readable medium or media.

54. The method of claim 53, wherein a reaction in said data structure is identified from an annotated genome.

55. The method of claim 54, further comprising storing said reaction that is identified from an annotated genome in a gene database.

56. The method of claim 53, further comprising annotating a reaction in said data structure.

57. The method of claim 56, wherein said annotation is selected from the group consisting of assignment of a gene, assignment of a protein, assignment of a subsystem, assignment of a confidence rating, reference to genome annotation information and reference to a publication.

58. The method of claim 53, wherein step (b)

further comprises identifying an unbalanced reaction in said data structure and adding a reaction to said data structure, thereby changing said unbalanced reaction to a balanced reaction.

59. The method of claim 53, wherein said adding a reaction comprises adding a reaction selected from the group consisting of an intra-system reaction, an exchange reaction, a reaction from a peripheral metabolic pathway, reaction from a central metabolic pathway, a gene associated reaction and a non-gene associated reaction.

60. The method of claim 59, wherein said peripheral metabolic pathway is selected from the group consisting of amino acid biosynthesis, amino acid degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, cofactor biosynthesis and transport processes.

61. The method of claim 53, wherein said *Homo sapiens* physiological function is selected from the group consisting of growth, energy production, redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor, transport of a metabolite, development, intercellular signaling, and consumption of carbon nitrogen, sulfur, phosphate, hydrogen or oxygen.

62. The method of claim 53, wherein said *Homo sapiens* physiological function is selected from the group consisting of degradation of a protein,

degradation of an amino acid, degradation of a purine, degradation of a pyrimidine, degradation of a lipid, degradation of a fatty acid and degradation of a cofactor.

63. The method of claim 53, wherein said data structure comprises a set of linear algebraic equations.

64. The method of claim 53, wherein said data structure comprises a matrix.

65. The method of claim 53, wherein said flux distribution is determined by linear programming.

66. A data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein said data structure is produced by a process comprising:

(a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of said *Homo sapiens* reactions;

(b) relating said plurality of *Homo sapiens* reactants to said plurality of *Homo sapiens* reactions in a data structure,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

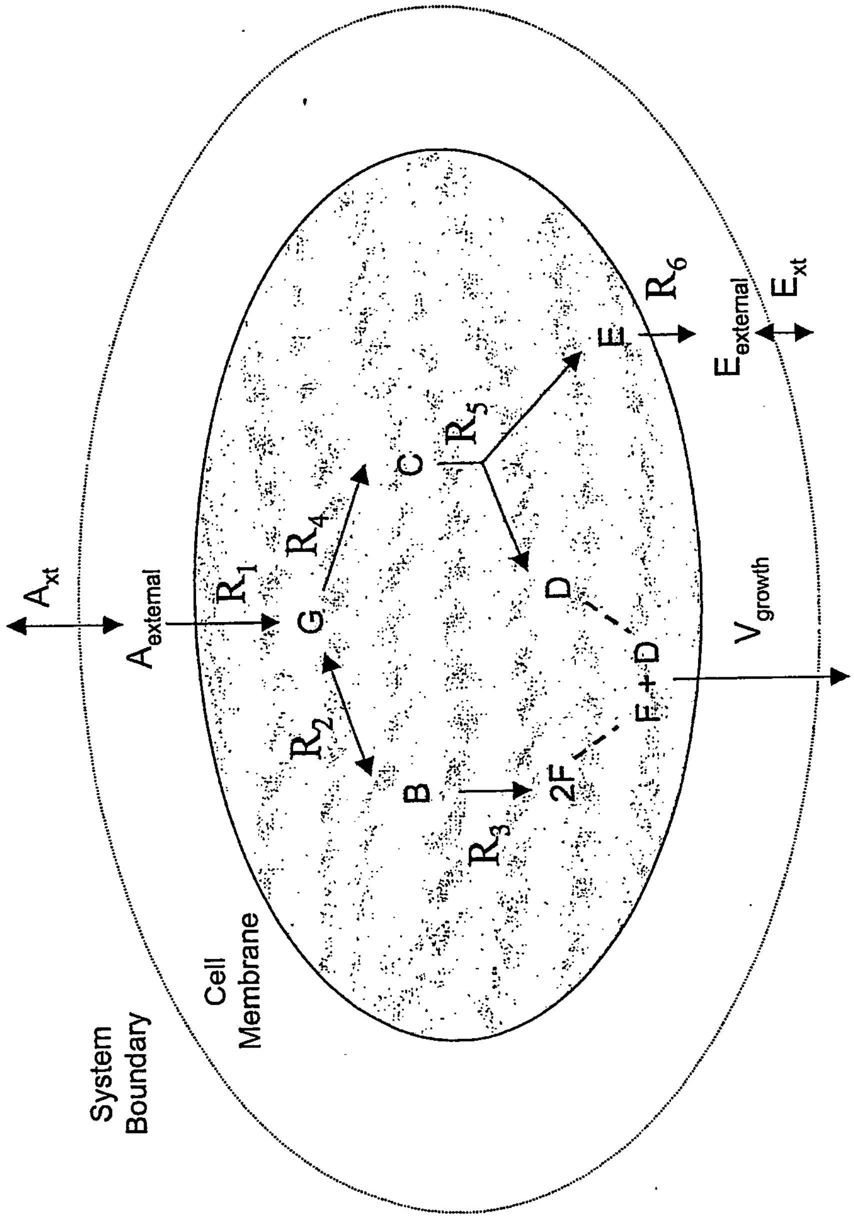
(c) determining a constraint set for said plurality of *Homo sapiens* reactions;

(d) providing an objective function;

(e) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, and

(f) if said at least one flux distribution is not predictive of *Homo sapiens* physiology, then adding a reaction to or deleting a reaction from said data structure and repeating step (e),

if said at least one flux distribution is predictive of *Homo sapiens* physiology, then storing said data structure in a computer readable medium or media.



System Boundary
Cell Membrane
A_{xt}
$A_{external}$
R_1
G
R_2
R_4
B
R_3
2F
C
R_5
D
F + D
E
R_6
$E_{external}$
E_{xt}
V_{growth}

FIGURE 1

Mass Balances	Flux Constraints
$G: R_1 - R_2 - R_4 = 0$ $B: R_2 - R_3 = 0$ $C: R_4 - R_5 = 0$ $D: R_5 - V_{growth} = 0$ $E: R_5 - R_6 = 0$ $F: 2R_3 - V_{growth} = 0$ $A_{external}: - A_{xt} - R_1 = 0$ $E_{external}: R_6 - E_{xt} = 0$	$0 \leq R_1 \leq \infty$ $-\infty \leq R_2 \leq \infty$ $0 \leq R_3 \leq \infty$ $0 \leq R_4 \leq \infty$ $0 \leq R_5 \leq \infty$ $0 \leq R_6 \leq \infty$ $0 \leq V_{growth} \leq \infty$ $Y_1 \leq A_{xt} \leq Y_1$ $-\infty \leq E_{xt} \leq 0$
Objective Function $Z = V_{growth}$	

FIGURE 2

$$
\begin{array}{c|ccccccccc}
 & R_1 & R_2 & R_3 & R_4 & R_5 & R_6 & V_{growth} & A_{xt} & E_{xt} \\
B & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\
C & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\
D & 0 & 0 & 0 & 0 & 1 & 0 & -1 & 0 & 0 \\
E & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 \\
F & 0 & 0 & 2 & 0 & 0 & 0 & -1 & 0 & 0 \\
G & 1 & -1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\
A_{external} & -1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \\
E_{external} & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1
\end{array}
\begin{bmatrix}
R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ V_{growth} \\ A_{xt} \\ E_{xt}
\end{bmatrix}
=
\begin{bmatrix}
0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0
\end{bmatrix}
$$

FIGURE 3

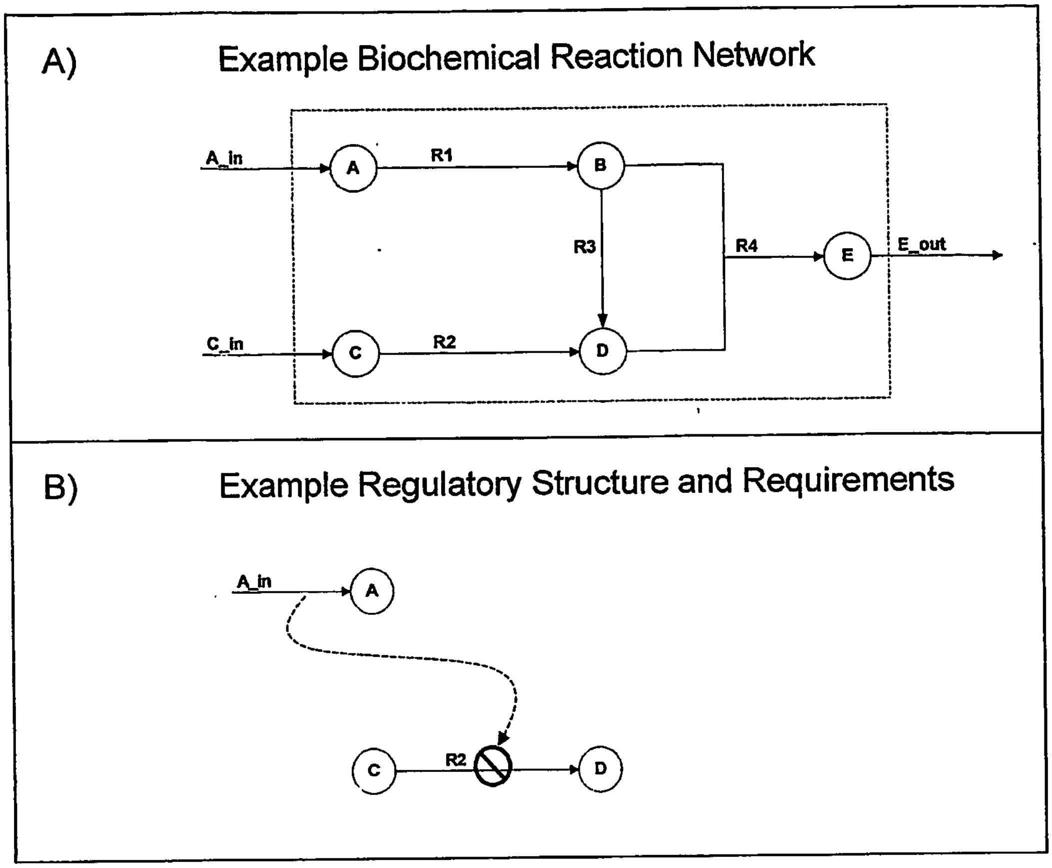

A)
Example Biochemical Reaction Network
A_in
A
R1
B
R3
R4
E
E_out
C_in
C
R2
D
B)
Example Regulatory Structure and Requirements
A_in
A
C
R2
D

FIGURE 4